Clinical Briefing
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I. INTEGRATED SUMMARY OF EFFICACY

I.A. SUMMARY

The co-primary efficacy endpoints of difference between treatments in mean change from baseline of trough $FEV_{1.0}$ and St. Georges Respiratory Questionnaire both succeeded in one study (039) out of the four pivotal trials. This definition of success is that the $FEV_{1.0}$ between treatments achieved statistical significance and the SGRQ achieved both the minimal clinically meaningful difference and statistical significance. During the 29 July, 1998 End Phase 2 Meeting, we devoted a great deal of time to the discussion of co-primary endpoints. The Agency suggested that $FEV_{1.0}$ be adopted as the single primary efficacy endpoint. GlaxoSmithKline opted to use the co-primary approach to satisfy the European CPMP but to adjust each endpoint for multiple comparisons so that each endpoint to could stand on its own. When the data were re-examined from the standpoint of only the trough $FEV_{1.0}$, two trials showed statistical significance of differences between treatments in mean changes from baseline of about 20 and 40 mL, both less than 3% of the baseline $FEV_{1.0}$.

Non-primary efficacy endpoints were also evaluated by repeated measures analyses, but the Type I Errors were not corrected for multiple comparisons of other endpoints within each study. Dozens of tests of inference were done in each study leading to gross study-wide Type I Error inflation. For this reason, inferential tests of significance will not be discussed for non-primary outcomes. These secondary and tertiary outcomes will be examined qualitatively in terms of direction and magnitude of difference, the latter only for those endpoints for which magnitude has meaning.

Two of the five secondary efficacy outcomes favored SB 207499 over placebo over all four pivotal trials: post-exercise breathlessness (modified Borg Scale) and 24-week exacerbation-free survival. Post-Exercise Breathlessness, on an 11-point modified Borg Scale, showed reductions from baseline (improvements) that were either larger in the SB 207499 group than in the placebo group (two trials), or showed in improvement while the placebo group showed a slight increase (worsening) (two trials). The 24-week exacerbation-free survival showed two studies in which SB 207499 was superior to placebo and two studies in which placebo barely edged out SB 207499. These data qualitatively favored SB 207499.

The magnitude of the difference between treatments in change from baseline for the trough FVC (<2% of baseline) was less than the relative magnitude of the change in the trough $FEV_{1.0}$. FVC and $FEV_{1.0}$ are two spirometric outcomes that are highly correlated, so the degree of support that the former could provide for the latter is small. The 11-point Summary COPD Symptom Score was comprised of summed scores for breathlessness, cough and sputum production. In the three studies in which it was performed, one favored superiority of the SB 207499 (091), one favored superiority of

the placebo (042) and, in the last (039), the two treatments were about equal. The overall outcome of the 6-Minute Walk indicated the equivalence of the two treatments in that some trials favored placebo, some favored SB 207499 and some were about equal.

Two tertiary endpoints were selected from the host of these that were measured because they are common endpoints in other studies of "obstructive" airways diseases and because they may represent real benefit to patients. These endpoints were rescue medication use in puffs/day and percent of symptom-free days. Both endpoints favored SB 207499 over placebo by a tiny margin in the three pivotal trials in which they were measured. Three other tertiary endpoints in three trials (039, 042, 091) provided some insight into acute efficacy and washout efficacy. There was no first-dose efficacy ($FEV_{1.0}$) that was measurable over the first four hours after taking the initial dose nor was there any diminution of efficacy for four hours after the last dose had been taken, comparing placebo to SB 207499.

At the end of the 24-Week double-blind treatment period in study 091, patients entered a 2-week randomized, double-blind, Run-Out phase. Patients initially randomized to SB 207499 15mg twice daily were re-randomized to either SB 207499 15mg twice daily (treatment sequence S/S) or placebo (treatment sequence S/P). Patients initially randomized to placebo continued to take placebo during the Run-Out phase (treatment sequence P/P). Differences between the mean trough $FEV_{1.0}$ at Week 24 and at Run-Out for each of the three assigned groups showed 10 ml declines for each of the three groups. Substituting placebo for SB 207499 at Run-Out was no different than continuing the SB 207499 and no different from continuing placebo treatment.

All endpoints, both primary and non-primary, were handled by repeated measures analyses that did not impute missing values and analyzed only the values available in the modified ITT group. The modified ITT group required a baseline value and at least one on-therapy efficacy evaluation during the double-blind period. This was interpreted to mean one on-therapy efficacy evaluation of the type being analyzed. $FEV_{1.0}$ was first measured at Week 1 and included more patients than the SGRQ, which was first measured at Week 12. It is likely that some of the diary data were available from Day 1. This suggests that no two endpoints were necessarily derived from the same modified ITT group. The drop-outs in these trials and the use of repeated measures analyses also weighted the outcome over the 24 weeks more heavily for the earliest time points.

I.B. DOSE-FINDING

Dose selection came from two Phase 2 studies that, together, included doses of 2.5, 5, 10 and 15 mg of SB 207499 twice daily. Both studies used very similar designs, patient populations and endpoints, though the only intent, here, is to examine results of both on the choice of dose based on the trough $FEV_{1.0}$. Study 038 was a randomized, placebo-controlled, double-blind, 4-week, 3 parallel-group study of COPD patients. The parallel groups were placebo, 2.5 or of 5 mg SB 207499 by mouth twice daily after food.

The primary efficacy endpoint was the difference between each SB 207499 dose and placebo in change from baseline to week 4 in trough $FEV_{1.0}$.

The baseline trough $FEV_{1.0}$ for each group and the change from baseline at each formal evaluation are presented below. A qualitative evaluation of the placebo group showed declines from baseline at all three visits. The two active treatment groups showed either an increase, decline or no change from baseline at the three visits. The change from baseline to week 4 of each active treatment group compared with placebo was not statistically significant, though the direction did reflect possible efficacy.

NDA #21573 (12/24/02, N-000) STUDY 038: TROUGH $FEV_{1.0}$ AT EACH VISIT IN ABSOLUTE UNITS OR AS CHANGE FROM BASELINE (L) [clinstat\038.pdf:68-9]

Visit	Placebo		2.5 mg		5 mg	
	n	Mean or Change from Mean	n	Mean or Change from Mean	n	Mean or Change from Mean
Baseline*	75	1.33	72	1.28	77	1.37
Week 1	70	-0.00	71	0.03	75	0.02
Week 2	70	-0.03	70	--0.02	73	0.00
Week 4	70	-0.03	70	0.00	73	-0.02
Endpoint	70	-0.03	71.	-0.00	75	-0.02
* in absolute units						

Study 032 was almost identical to 038 except that it included three doses of SB 207499 (5, 10 or 15 mg), six weeks of double-blind follow-up and the primary efficacy endpoint was difference between each SB 207499 dose and placebo in change from baseline to week 6 in trough $FEV_{1.0}$.

The baseline trough $FEV_{1.0}$ for each group and the change from baseline at each formal evaluation are presented below. A qualitative evaluation of the placebo group showed declines from baseline at all visits. The active treatment groups showed mostly increases from baseline for all doses of SB 207499. The change of each of the two lower doses of active treatment compared with placebo from baseline to week 6 was not statistically significant. The difference in change from baseline compared with placebo of all three doses of SB 207499 did reflect possible efficacy but there was no dose-ordering. The 15 mg twice daily dose did achieve statistical significance in change from baseline to week 6 in trough $FEV_{1.0}$ compared with placebo. The magnitude of change from baseline (130 mL, 9.8%) was respectable.

NDA #21573 (12/24/02, N-000) STUDY 032: TROUGH $FEV_{1.0}$ AT EACH VISIT IN ABSOLUTE UNITS OR AS CHANGE FROM BASELINE (L) [clinstat\032.pdf:75]

Visit	Placebo		5 mg		10 mg		15 mg	
	n	Mean or Change from Mean	n	Mean or Change from Mean	n	Mean or Change from Mean	n	Mean or Change from Mean
Baseline*	106	1.37	109	1.31	102	1.37	107	1.32
Week 1	105	-0.02	105	0.04	98	0.03	105	0.06
Week 2	100	-0.02	99	0.07	89	0.02	98	0.09

NDA #21573 (12/24/02, N-000) STUDY 032: TROUGH $FEV_{1.0}$ AT EACH VISIT IN ABSOLUTE UNITS OR AS CHANGE FROM BASELINE (L) [clinstat\032.pdf:75]								
	Placebo		5 mg		10 mg		15 mg	
Visit	n	Mean or Change from Mean	n	Mean or Change from Mean	n	Mean or Change from Mean	n	Mean or Change from Mean
Week 4	95	-0.01	96	0.06	87	0.02	95	0.09
Week 6	91	-0.03	95	0.02	85	-0.01	90	0.13
Endpoint	105	-0.02	105	0.04	98	-0.00	105	0.12
* in absolute units								

I.C. THE FOUR PIVOTAL TRIALS

I.C.1. PRIMARY EFFICACY ENDPOINTS

Twenty-four weeks of SB 207499 treatment were evaluated in four pivotal, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies (039, 042, 091, and 156). The primary objectives of the four pivotal studies were to assess the clinical efficacy of oral SB 207499 15mg twice daily twice daily by means of the trough forced expiratory volume in 1 second ($FEV_{1.0}$) and total score of the St. George's Respiratory Questionnaire (SGRQ) over 24 weeks in patients with COPD. The assessment of the effect of SB 207499 on COPD exacerbations was a secondary objective in all four pivotal studies.

In the pivotal studies, SB 207499 15mg twice daily was compared to placebo in a 1:1 (Study 156) or 2:1 (Studies 039, 042, and 091) randomization ratio in populations ranging from 647 to 825 patients per study. Each study had a 4-week, single-blind, placebo run-in period followed by 24 weeks of double-blind treatment. One tablet of SB 207499 15 mg or matched placebo was taken twice daily, immediately after breakfast and after the evening meal, in order to improve gastrointestinal tolerability. The treatment period was followed by a 1-week safety follow-up period for patients who did not enter an open-label extension or who withdrew prior to the end of the study. In Study 091 only, there was an additional 2-week double-blind, placebo-controlled, randomized withdrawal phase to assess the maintenance of effect following discontinuation of treatment.

The following concomitant COPD medications were permitted during the studies: stable doses of anticholinergic medication via a metered dose inhaler (MDI), albuterol/salbutamol (on an "as needed" basis) via MDI with or without a spacer (according to the patient's usual practice), and mucolytics. Additional COPD medications were allowed for less than 14 days to treat COPD exacerbations.

To be eligible for participation patients had to be diagnosed with COPD (by American Thoracic Society or European Respiratory Society definitions), be from 40 to 80 years of age, have a cigarette smoking history of $\geq$10 pack years. Patients were required to have a pre-bronchodilator $FEV_{1.0}$ to FVC ratio of $\leq$0.7, bronchodilator $FEV_{1.0}$

reversibility of ≤15% or ≤200mL, and post-bronchodilator $FEV_{1.0}$ between 30% and ≤70% (inclusive) of predicted normal at Screening.

The following medications were prohibited throughout the pivotal studies except for the short-term (<2 weeks) management of COPD exacerbations: corticosteroids (inhaled or oral), inhaled cromolyn sodium or nedocromil, inhaled long-acting beta-2 agonists, inhaled short-acting beta–2 agonists other than albuterol/salbutamol, oral or nebulized beta-2 agonists, nebulized anticholinergics, and/or leukotriene modifiers. Combination beta-2 agonist/anticholinergic therapy was not permitted during the studies and was changed to separate, single-therapy inhalers prior to or at Screening. Theophylline was not permitted at any time during the pivotal studies.

The primary efficacy variables were the effect of SB 207499 on pulmonary function measured as the mean change from Baseline in trough $FEV_{1.0}$ and in total score of the SGRQ averaged over 24 weeks. Secondary measures of efficacy were COPD exacerbation rates, forced vital capacity (FVC), summary symptom score, exercise tolerance, and post-exercise breathlessness. Summary symptom scores were assessed in Study 156 in a manner that made them non-comparable with the three other pivotal trials (investigator recorded, different size scale, comprised of different numbers of symptoms).

Evidence for the efficacy of SB 207499 in COPD was primarily provided by the statistical analyses performed individually for the four pivotal studies (039, 042, 091, and 156). Primary efficacy results were presented based on the average change from Baseline over the 24 week double-blind treatment period. For individual study results from North America Studies 039 and 156, the repeated measures model included treatment, center, and time as fixed effects. For individual Europe Studies 042 and 091, the model included treatment, country, and time as fixed effects.

The following table shows the results of the primary endpoints analyses for the four pivotal trials. The adjusted mean changes from baseline of both co-primary endpoints for the pivotal trials is bolded in columns titled "Mean Diff." The endpoint that was tested was the adjusted mean difference in changes from baseline and is approximately the difference between placebo and SB 207499 "Mean Diff" values.

NDA #21573 (12/24/02, N-000) INTEGRATED SUMMARY OF EFFICACY (ISE): BASELINE AND MEAN CHANGE FROM BASELINE FOR PRIMARY EFFICACY ENDPOINTS OF THE PHASE 3 PIVOTAL TRIALS
[clinstat\ise\ise.pdf:56, 64]

	039		042		091		156	
Treatment	**Baseline**	**Mean Diff**	**Baseline[1]**	**Mean Diff**	**Baseline[1]**	**Mean Diff**	**Baseline[1]**	**Mean Diff**
$FEV_{1.0}$ (L)								
Placebo	1.42	**-0.03**	1.36	**-0.00**	1.44	**-0.03**	1.38	**-0.02**
SB 207499	1.34	**0.01**	1.38	**0.03**	1.45	**0.00**	1.36	**0.01**
SIGNIFICANT		Yes		No		No		Yes
SGRQ (101-point scale 0-100)								
Placebo	44.8	**0.4**	45.9	**-4.9**	42.1	**-2.3**	43.2	**-1.3**
SB 207499	45.1	**-3.7**	43.8	**-4.2**	42.7	**-2.7**	*44.4*	**-3.2**
SIGNIFICANT[2]		Yes		No		No		Yes

NDA #21573 (12/24/02, N-000) INTEGRATED SUMMARY OF EFFICACY (ISE): BASELINE AND MEAN CHANGE FROM BASELINE FOR PRIMARY EFFICACY ENDPOINTS OF THE PHASE 3 PIVOTAL TRIALS [clinstat\ise\ise.pdf:56, 64]								
	039		042		091		156	
Treatment	Baseline	Mean Diff	Baseline[1]	Mean Diff	Baseline[1]	Mean Diff	Baseline[1]	Mean Diff
MID[3]		Yes		No		No		No

[1] Approximate baseline taken from another analysis of the same endpoint with a similar "n" at baseline.
[2] Statistically significant difference in mean change from baseline between treatments by repeated measures analysis with the modified Bonferroni Type I Error adjustment procedure of Hochberg.
[3] Minimum Important Difference (4.0)

I.C.1.a. $FEV_{1.0}$

There are fairly consistent findings of differences between treatments in mean changes from baseline in $FEV_{1.0}$ for the pivotal trials of 20 to 40 mL. These difference in mean changes from baseline were mostly due to small increases in the SB 207499 group and small, but somewhat larger, decreases in the placebo group. The declines in the placebo group that mostly drove the differences in three of the trials occurred over 2-4 weeks in two of them (039, 091) and over 4 weeks with additional decline at the fifth and sixth month in the third (156). In only one study (042) was the difference in changes from baseline driven by the efficacy of SB 207499 and the increase in that group occurred over 12 weeks. These differences between groups in changes from baseline are tiny indeed. The largest of these mean differences from baseline between groups (40 mL) represents less than a 3% change in a baseline $FEV_{1.0}$ of 1.40 L.

GlaxoSmithKline points out that the magnitude of the $FEV_{1.0}$ response at endpoint (last visit or study termination) was larger than the average change and it was. Two trials showed a difference in mean change from baseline to endpoint of 40 mL (042, 156), one showed a difference of 30 mL (091) and one showed an 80 mL difference (039). Three trials represent less than a 3% difference between groups in changes from baseline and the largest difference between groups was less than a 6% difference between groups [clinstat\ise\ise.pdf:18]. It should also be noted that endpoint analysis is similar to LOCF analysis in that the endpoint is the last on-therapy observation. There is no reason to expect endpoint analysis to provide the same estimate of magnitude of effect as the repeated measures analysis, but it is the latter that the sponsor prospectively chose to analyze the primary efficacy endpoints.

I.C.1.b. ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

The SB 207499 treatment group in Study 039 demonstrated a clinically meaningful improvement of -4.09 points in total score of the SGRQ relative to placebo that was statistically significant when averaged over 24 weeks. None of the remaining three trials approached a minimal clinically meaningful difference though one of them (156) did produce a statistically significant outcome. When difference in change from baseline at endpoint between groups was examined, only 039 achieved a minimally clinically meaningful outcome.

Dr. Paul Jones, developer of the SGRQ, has submitted his assurance that the translations that he provided of the instrument to GlaxoSmithKline were validated versions. GlaxoSmithKline has also submitted a psychometric evaluation of the instrument in most of the countries in which it was used, drawn from studies submitted with the NDA. Details about linguistic and cultural validation of those translations in the refereed medical literature were not provided [clinstat\039.pdf:3, clinstat\042.pdf:3, clinstat\091.pdf:3, clinstat\156.pdf:13, clinstat\168.pdf:3, 7/25/03 Attachment I.pdf:1, Attachment II.pdf:1-14, Attachment III.pdf:1-3].

I.C.2. SECONDARY EFFICACY ENDPOINTS

These were also evaluated by repeated measures analyses, but the Type I Errors were not corrected for multiple comparisons of other endpoints within each study. Dozens of tests of inference were done which would lead to study-wide Type I Error inflation if the uncorrected probabilities were given any weight. For example, only 12 tests of inference would raise the study-wide Type I Error to < 0.46, based on the assumption of independence of outcomes. For this reason, no inferential results will be addressed in this section and these secondary outcomes will be examined qualitatively in terms of direction and magnitude of difference. The five secondary outcomes in three trials (039, 042, 091) and the three secondary outcomes and one tertiary outcome in the fourth trial (156) are shown in the following table.

NDA #21573 (12/24/02, N-000) INTEGRATED SUMMARY OF EFFICACY (ISE): BASELINE AND MEAN CHANGE FROM BASELINE FOR ALL SECONDARY EFFICACY ENDPOINTS OF THE PHASE 3 PIVOTAL TRIALS

	039		042		091		156[2]	
Treatment	**Baseline[1]**	**Mean Diff**	**Baseline[1]**	**Mean Diff**	**Baseline[1]**	**Mean Diff**	**Baseline[1]**	**Mean Diff**
TROUGH FVC (L)								
Placebo	2.90	**-0.05**	2.75	**-0.02**	2.82	**-0.02**	2.75	**-0.02**
SB 207499	2.73	**-0.00**	2.76	**0.02**	2.83	**-0.01**	2.69	**0.00**
POST-EXERCISE BREATHLESSNESS (MODIFIED BORG SCALE, 11 points, 0-10 scale)								
Placebo	3.40	**0.07**	3.54	**-0.16**	3.80	**0.00**	3.22	**0.05**
SB 207499	3.37	**-0.17**	3.73	**-0.36**	3.69	**-0.16**	*3.37*	***-0.10***
SUMMARY DIARY COPD SYMPTOM SCORE (11 points, 0-10 scale)								
Placebo	4.54	**-0.20**	4.77	**-0.50**	4.42	**-0.25**	n/a	n/a
SB 207499	4.45	**-0.22**	4.71	**-0.33**	4.47	**-0.36**	n/a	n/a
6-MINUTE WALK (meters)								
Placebo	347.3	**6.3**	397.6	**14.1**	421.8	**7.3**	369.8	**2.8**
SB 207499	340.2	**14.2**	421.1	**3.8**	431.2	**5.1**	364.7	**7.9**
PERCENT OF PATIENTS COPD EXACERBATION-FREE THROUGH 24 WEEKS (% of patients in treatment group)								
Placebo	100.0	**62.4**	100.0	**61.3**	100.0	**51.1**	100.0	**67.4**
SB 207499	100.0	**74.0**	*100.0*	**58.8**	100.0	**63.9**	100.0	**66.7**

[1] Approximate baseline taken from another analysis of the same endpoint with a similar "n" at baseline.
[2] The 6-minute walk in this study was designated as a tertiary efficacy endpoint instead of as a secondary endpoint.
n/a = Not Applicable

Trough Forced Vital Capacity (FVC) showed differences between treatments in mean changes from baseline of 10 to 50 mL from a baseline of about 2.75 L (maximum

difference < 2%). This difference favored FVC reduction in the placebo group and less reduction, stabilization or increase in the SB 207499 group.

Post-exercise breathlessness on an 11-point modified Borg Scale showed decreases (improvements) that were greater for the SB 207499 group than for the placebo group. In two trials (039, 156), the placebo group increased (worsened) slightly by this measure.

The 11-point COPD Summary Symptom Score summed the scores of breathlessness (0-4 scale), cough and sputum production (each on a 0-3 scale). Both treatment groups decreased (improved) in changes from baseline by this measure. In trial 042, the placebo group actually showed a greater decrease (improvement) than did the SB 207499 group.

The 6-Minute Walk test showed mean changes from baseline that sometimes favored SB 207499 (039) and more of the time favored placebo (042, 091). The maximum adjusted mean difference between treatment groups favoring SB 207499 was 7.9 meters over a baseline of about 345 meters (difference < 3%).

The percent of patients who were COPD Exacerbation-Free Through 24 Weeks showed slight differences between treatment groups. In two trials, this measure favored SB 207499 (039, 091) and, in the other two, it favored the placebo group (042, 156).

I.C.3. TERTIARY EFFICACY ENDPOINTS

A host of tertiary efficacy variables were specified, but only two were chosen for review here: rescue medication use and symptom-free days. The rationale for choosing these outcomes include: they are common endpoints in other studies of "obstructive" airways diseases and they may represent some real benefit to the patients.

In each of the three trials in which it was determined, the number of puffs/day of rescue medicine use expressed as a change from baseline was greater in the placebo group than in the SB 207499 group. These differences were small ranging from 0.02 to 0.21 puffs/day, or from 4 to 36 total puffs of rescue medication over the 168-day, 24-week treatment period.

NDA #21573 (12/24/02, N-000) INTEGRATED SUMMARY OF EFFICACY (ISE): BASELINE AND MEAN CHANGE FROM BASELINE FOR SELECTED TERTIARY EFFICACY ENDPOINTS OF THE PHASE 3 PIVOTAL TRIALS								
	039		042		091		156	
Treatment	Baseline	Mean Diff	Baseline	Mean Diff	Baseline	Mean Diff	Baseline	Mean Diff
RESCUE MEDICATION USE (mean puffs/day)								
Placebo	3.56	**0.24**	3.41	**0.08**	2.62	**0.15**	n/a	n/a
SB 207499	3.63	**0.09**	3.28	**0.06**	2.73	**-0.06**	n/a	n/a

.. In each of the three trials in which it was measured, the percent of symptom free days was greater for the SB 207499 group than for the placebo group. Though consistent, these differences were small ranging from 0.6 to 0.9 percent symptom free days, or from 1 to 1.5 symptom free days over the 168-day, 24-week treatment period.

NDA #21573 (12/24/02, N-000) INTEGRATED SUMMARY OF EFFICACY (ISE): BASELINE AND MEAN CHANGE FROM BASELINE FOR SELECTED TERTIARY EFFICACY ENDPOINTS OF THE PHASE 3 PIVOTAL TRIALS

	039		042		091		156	
Treatment	**Baseline**	**Mean Diff**	**Baseline**	**Mean Diff**	**Baseline**	**Mean Diff**	**Baseline**	**Mean Diff**
SYMPTOM-FREE DAYS (mean % of treatment days)								
Placebo	n/a	**1.1**	n/a	**2.2**	n/a	**1.8**	n/a	n/a
SB 207499	n/a	**1.7**	n/a	**3.1**	n/a	**2.6**	*n/a*	*n/a*

n/a = not applicable

II. INTEGRATED SUMMARY OF SAFETY

II.A. SUMMARY

In round numbers, over 6500 patients have participated in SB 207499 COPD and asthma, controlled and uncontrolled trials. Over 4400 patients have been exposed to SB 207499, 2119 COPD patients in controlled trials, 1069 COPD patients in uncontrolled trials and 764 asthma patients in controlled trials. The vast majority of these patients received a dose of 15 mg given twice daily. The demographic characteristics of patients in all controlled studies were reflective of the inclusion/exclusion criteria of the studies and were generally similar across all SB 207499 treatment groups and placebo. Overall, the mean age of all patients treated with SB 207499 was 59.4 years, which was similar to the mean age (61.0 years) of the placebo-treated patients. The majority of the SB 207499-treated (67.4%) and placebo-treated (68.2%) were male, and the great majority of all SB 207499-treated (96.1%) and placebo-treated (96.2%) patients were Caucasian. Smoking history, characterized by pack years, was similar between SB 207499-treated (48.0 pack years) and placebo-treated (49.8 pack years) patients. In all controlled and uncontrolled trials, 685 patients received SB 207499 for 6 months, 602 for 12 months and 539 for 18 months.

Nausea, diarrhea, abdominal pain, dyspepsia and vomiting were among the eight most frequent adverse events (AEs) reported in controlled trials and all were 2-3 fold more frequent, corrected for numbers randomized to each treatment, in patients who took SB 207499 than placebo. The three other AEs in the eight were COPD, upper respiratory infection (URI) and headache, which were about equally frequent in patients taking placebo and SB 2207499. Uncontrolled trials enrolled patients from prior efficacy trials who had taken either SB 207499 or placebo and gave both groups SB 207499. Uncontrolled trials showed that the abdominal complaints of nausea, vomiting, dyspepsia, abdominal pain and diarrhea were all less frequent in patients who had prior treatment with SB 207499. Perhaps those patients who previously received SB 207499 and were able remain on it for the duration of the feeder studies were more tolerant of abdominal complaints than those whose first exposure to SB 207499 was in the uncontrolled studies. Somewhat curiously, patients who had previously received SB 207499 also had more frequent AEs that were chronic obstructive airways disease and respiratory disorder. This is exactly the reverse of what one would expect from an effective treatment of COPD unless a selection bias for that prior treatment-group in the uncontrolled trials or tachyphylaxis had occurred.

There were 17 deaths, from placebo run-in through post-therapy periods in all controlled trials. One patient committed suicide during the run-in. Seven on-therapy, double-blind-period fatal AEs occurred, one in the placebo group and six in the SB 207499 group. Nine patients died during the post-therapy period, five from the placebo group and four from the SB 207499 group. All of these on-therapy and post-therapy deaths were in patients with COPD and all were due to atherosclerotic vascular or

pulmonary diseases. The frequency of females dying (23.5%) was slightly lower than expected, compared with the demographics of female gender participation (32.6%). In the uncontrolled trials, 24 patients died during treatment with SB 207499 (8 patients) or after discontinuing treatment (16 patients). The most striking finding was the relatively few female deaths (2/24 = 8.3%) compared with the demographics of female gender participation (22.2%) in all uncontrolled trials.

Total patients reporting serious adverse events (SAEs) in controlled trials were slightly more frequent in the placebo group (6.1%) than in all groups exposed to SB 207499 (4.3%). We focused on those SAEs that were more frequent in the high-dose SB 207499 group than in the placebo group. All SAEs that fit this criterion had a frequency of much less than 1% yielded by very small numbers of patients for each SAE and had no apparent unifying theme. This suggests that SAEs were not disproposrtionately associated with SB 207499. Two hundred seventy-three patients (25.3% of the 1078 enrolled patients) had one or more SAEs during the uncontrolled studies. Nearly all SAEs were events that are commonly observed in a population of older patients. The numbers and patterns of SAEs did not differ by prior treatment with SB 207499 or placebo.

Withdrawals due to AEs in controlled trials were dominated by many-fold greater frequency in the high-dose SB 207499 group (15 mg twice daily) than in the placebo group. The five most frequent were nausea (placebo 0.4%, SB 207499 15.7%), abdominal pain (placebo 0.5%, SB 207499 4.6%), diarrhea (placebo 0.4%, SB 207499 3.6%), vomiting (placebo 0.2%, SB 207499 3.3%), and dyspepsia (placebo 0.1%, SB 207499 1.0%). The numbers of patients with the SAE was expressed as a percent of the number of patients randomized to each treatment group. In the uncontrolled trials, there were twice as many withdrawals due to adverse events in patients previously treated with placebo than with SB 207499. The withdrawals due to adverse events in the uncontrolled trials for GI adverse events also were more frequent in patients previously treated with placebo than with SB 207499. This latter observation is a repetition of a similar finding for all adverse events in these uncontrolled trials suggesting that patients who previously received SB 207499 and were able remain on it for the duration of the feeder studies were not as susceptible to the abdominal complaints as those whose first exposure to SB 207499 was in the uncontrolled studies.

The concept of gastrointestinal adverse events (GIAEs) of concern was designed to single out these cases for thorough evaluation. Mesenteric arteritis seen in rats during the earliest pre-clinical studies was a worrisome and largely unmonitorable adverse event. A plan was devised to evaluate one of the only not-immediately-fatal, possibly-monitorable consequences of mesenteric arteritis, ischemic colitis. The intent was to monitor fecal occult blood (FOB) and orthostatic changes, within a short time after the event and daily until resolution. The FOB was to signal the need for a colonoscopy and the orthostatic changes were to alert the investigator to possible acute volume depletion that might signal frank bowel infarction.

Complete evaluation of the colon is widely supported as a routine surveillance method to identify adenomas/adenocarcinomas of the colon in asymptomatic patients over the age of 50 years. The use of colonoscopy for cancer surveillance is recommended as a routine measure by many professional societies and organizations. It was felt that melena, bright red blood *per rectum* or a positive FOB in a patient population of this age would be adequate justification for a colon evaluation under normal clinical conditions and would represent "usual care." Complete evaluation of the colon showing no changes consistent with ischemic colitis in a large number of patients might provide reassurance of the absence of mesenteric arteritis.

Investigators identified GIAEs of concern based on patient reports of GI symptoms (e.g., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhea, or vomiting) that caused the patient to be concerned or interfered with their activities (including eating and sleeping). The investigator was to complete a clinical assessment of each such GI symptom reported within 24 hours of its occurrence. When a GI symptom of concern to the patient was reported, the patient was asked to use a previously provided fecal occult blood (FOB) test kit and to schedule a clinic visit within 24 hours. Failure to provide a FOB specimen was to trigger a rectal examination with FOB testing at the first clinic visit.

In Phase 3 controlled trials, about a three-fold greater frequency of GIAEs of concern (corrected for numbers of patients in each treatment group) were reported in patients treated with SB 207499, 15 mg twice daily, 264 (12.5%) than were reported in patients treated with placebo 56 (4.2%). In addition, a little less than twice the frequency of patients treated with SB 207499 who reported GIAEs of concern were considered related to the treatment (76.9%) compared with placebo (44.6%).

A total of 154 (58%) of the 264 patients treated with SB 207499 15 mg twice daily who reported one or more GIAEs of concern also had accompanying FOB tests performed within 14 days of reporting a GIAE of concern. Of these 154 patients, 15 (9.7%) of patients had a positive test result. A total of 31 (55%) of the 56 placebo-treated patients who reported at least one GIAE of concern also had accompanying FOB tests performed within 14 days of reporting a GIAE of concern and 6 (19.4%) of 31 patients tested positive for fecal occult blood. This failure to follow up GIAEs of concern with timely FOB testing represents quite a departure from both the protocols and the rigor that we expected would be brought to bear on this subset of patients.

In all Phase III COPD studies, routine FOBs were conducted at Screening and at the end of the treatment period or early withdrawal. In addition, FOBs were supposed to have been conducted for all GIAEs of concern within 24 hours of the event. A total of 49 patients who were FOB-negative at baseline became FOB-positive sometime during the double-blind period. This was presented as a set of limited narratives and the following table was extracted from them. About half of the patients developing a positive FOB

during treatment reported frank melena and these were distributed with about the same frequency between both treatment groups (n.b. 2:1 randomization in most Phase 3 studies). Disturbingly, 15 of the 23 patients reporting melena were NOT included in the category of gastrointestinal adverse events (GIAE) of concern. Even more disturbing is that only 5 of the 23 elderly patients reporting melena were evaluated by a colonoscopy.

NDA #21573 (12/24/02, N-000) ISS: REPORTING AND EVALUATION OF COPD PATIENTS WITH POSITIVE FECAL OCCULT BLOOD DURING TREATMENT WHO WERE NEGATIVE AT BASELINE, PHASE 3 STUDIES
[clinstat\iss\iss.pdf:336-41, 1/24/03 update\120 day safety update.pdf:140-5]√

Measure	Placebo	SB 207499 15 mg twice daily
Total FOB- Positive Patients	16	33
number of FOB-positive stool samples	31	67
patients with at least one GIAE of concern	7	15
patients with melena	8	15
patients with melena NOT reported as a GIAE of concern	6	9
patients receiving colonoscopy	2*	3**

* one patient for melena, the other for abdominal pain
** one for hemorrhoids, one for melena and abdominal pain and one for melena alone

A total of 888 (82.4%) of 1078 patients had routine FOB tests during the uncontrolled studies. About twice the frequency of prior SB 207499 treated patients (30 patients, 5.1%), compared with prior placebo-treated patients (8 patients, 2.7%) transitioned from negative at baseline to positive sometime during uncontrolled therapy, but the numbers and percentages were small.

A total of 157 (59%) patients treated with SB 207499 15 mg twice daily who reported one or more GIAEs of concern and 42 (75%) patients treated with placebo who reported one or more GIAEs of concern also had accompanying orthostatic vital sign changes "of concern" (i.e., pre-defined systolic and diastolic blood pressures and heart rate changes) evaluation.

Colonoscopy reports were presented in the Integrated Summary of Safety, but only from one of the pivotal trials, one cardiac safety study and the two long-term safety extension studies. Events that occurred during Studies 156 and 168 resulted in 19 patients having colonoscopies performed. Ten of these patients (4 placebo-treated and 6 SB 207499-treated patients) who had a colonoscopy performed experienced at least one GIAE of concern. Only four of these ten colonoscopies were carried out within four weeks after the GIAE of concern and only two colonoscopies were performed within two weeks of the signal event. Of the remaining 9 colonoscopy patients, 6 patients with AEs in the GI body system that were not considered GIAEs of concern had colonoscopies performed, including 2 placebo-treated and 4 SB 207499-treated patients. A total of 3 patients with gastrointestinal symptoms that were not reported as adverse events had colonoscopies performed (2 placebo-treated and 1 SB 207499-treated patient). Of the 11 SB 207499 treated patients who had colonoscopies, none reported lesions consistent with ischemic colitis. Thirteen patients from uncontrolled long-term safety studies, 040 and

041, who had GIAEs of potential concern also underwent colonoscopies and there were no reports of lesions consistent with ischemic colitis.

There were no pregnancies in controlled and uncontrolled studies, which is not too surprising considering the age range of these patients. Clinical laboratory results in clinical trials included: a complete blood count (CBC) with platelets and limited white blood cell count (WBC) differential and selected chemistries (AST, ALT, GGT, total bilirubin, alkaline phosphatase, BUN, creatinine, sodium (Na), potassium (K), glucose and uric acid). These were presented as shift tables of the number (%) or patient who were normal at baseline and who later fell into one of five categories: low values of concern, low values, normal values, high values and high values of concern. Vital signs (pulse rate, systolic and diastolic blood pressure) were similarly examined for categorical changes from normal at baseline during the double-blind treatment period. All of these categories were pre-defined for each variable. No consistent or large differences from placebo were noted for patients treated with SB 207499 15 mg twice daily in vital signs, hematology or chemistry laboratory values in controlled or uncontrolled trials.

Cardiovascular safety was one of the four preclinical signals of concern and was the sole subject of one trial (168) but was monitored by electrocardiograms (ECGs) in many other trials. A 12-lead ECG was obtained during run-in visits and double-blind treatment periods, early withdrawal and at the safety follow-up. More than 70,000 ECGs were obtained for analysis across the SB 207499 asthma and COPD programs including the uncontrolled long-term safety extension studies. Various variables were derived from the ECGs and included: QRS interval, PR interval, atrial rate, ventricular rate, QTc (Bazett's) interval, QTc (Bazett's) change from baseline and QT uncorrected. All of these involved patients with normal baseline values whose most extreme findings during the double-blind period were rated in the same five predefined categories used for hematology, chemistry and vital sign reporting. QRS axis was unique in that it had only three double-blind treatment categories and these were right axis deviation (RAD), left axis deviation (LAD) and normal axis. These shift tables compared the placebo treatment to controlled trial treatment with SB 207499 at a dose of 15 mg twice daily. Several interesting anomalies in these data were discussed but the final conclusion was that nothing of consequence was found in controlled or uncontrolled clinical trials.

An analysis of CMax ECG variables obtained at 3 hours post-dose on Day 1 and Week 24 was performed for the Phase III pivotal studies. ECGs were not obtained at C_{Max} in the mechanism of action studies. The trough CMax ECGs were largely unrevealing of any discrepancy between the high-dose (15 mg twice daily) SB 207499 group and the placebo group and did not confirm any of the small anomalies seen in the non-trough ECG analyses. There have been several publications demonstrating the utility of the T-wave axis as an indicator of risk of cardiac events in elderly people in population-based studies. The utility of this measurement in trials of short duration is unknown. Analyses of all T-wave axis data were presented for the Phase 3 pivotal studies (039, 042, 091, 156), the cardiovascular safety study (168) and the long-term safety extension studies (040, 041). Changes of concern in T-wave axis were defined as

a change from baseline in T-wave axis of ≥ 30 degrees and a T-wave axis outside of the normal range (< -15 degrees or > +105 degrees) at baseline. This exploratory analysis was not revealing of a safety signal in the SB 207499 high-dose (15 mg twice daily) group.

Integrated Holter monitoring data was found in Study 168 incorporating uniform Holter criteria and narratives for all patients with Holter values of concern. Accelerated idioventricular rhythm/idioventricular rhythm, atrial fibrillation, atrial flutter, Mobitz Type I 2nd degree AV block, sinus bradycardia and ventricular tachycardia were all more frequently found in the SB 207499 group than in the placebo group but numbers were tiny, in single digits. The strongest outcome variables for both of these populations were the more frequent findings of accelerated idioventricular rhythm/ideoventricular rhythm and sinus bradycardia in the SB 207499 group, a mechanistically contradictory set of events.

II.A.1. OVERVIEW

To date, the SB 207499 clinical development program includes 66 studies, 12 of which were conducted in COPD patients and 4 in asthma patients. Four of the twelve COPD studies were adequate and well-controlled studies, hereafter referred to as the "pivotal studies." Six of the twelve COPD studies were supporting studies, and two were open-label long-term extension studies. Of the twelve COPD studies, ten trials were placebo-controlled studies and two trials were uncontrolled long-term studies [clinstat\iss\iss.pdf:24, 136].

Safety data from the study grouping "all controlled trials" were analyzed with the goal of assessing the comparative safety of SB 207499 to placebo across all controlled studies. This grouping includes all patients from controlled Phase II and Phase III studies in COPD and asthma patients (Studies 005, 007, 022, 032, 038, 039, 042, 076, 077, 091, 110, 111 and 156). In the ISS, safety results are presented for the safety population. The safety population consisted of all randomized subjects who had taken at least one dose of study drug. A subject was included in all the analyses for which data were available. One small crossover study (Study 008), which enrolled a low number of patients was not included in the ISS. Inclusion of asthma patients was requested by the FDA. [clinstat\iss\iss.pdf:28, 140, 1/24/03 update\120 day safety update.pdf:25].

The 120-Day Safety Update added to that safety information submitted to the FDA on 23 December 2002 in this New Drug Application. The principal additions to the SB 207499 integrated safety database are safety data from the completed Phase III Study 168, a safety study conducted primarily to evaluate safety data from 24-hour continuous ambulatory electrocardiography (Holter) monitoring. Safety data from Study 168 were not integrated in the ISS; however, all Holter data from Studies 039, 042, 091, and 168 were presented in Appendix J of the Study 168 clinical study report as the integrated Holter data from all trials in which Holters were performed. This Safety Update includes

safety data from several ongoing studies (Studies 040, 041, 107, 122, 150, 157, 165, 167, and 168) [1/24/03 update\120 day safety update.pdf:25, 147, clinstat\168.pdf:1527].

NDA #21573 (12/24/02, N-000) ISS: SUMMARY INFORMATION ON STUDY CHARACTERISTICS [clinstat\iss\iss.pdf:137, 1/24/03 update\120 day safety update.pdf:34-5]√

Number	Length	Groups	SB Doses (mg bid)	Design	Location	Patients Randomized	
						Placebo	SB 207499
COPD PIVOTAL EFFICACY STUDIES					**totals =**	**1091**	**1792**
039	24 wks	SB, Pbo	15	DB, PC, R, PG	N America[b]	216	431
042	24 wks	SB, Pbo	15	DB, PC, R, PG	Europe[c]	226	474
091	24 wks	SB, Pbo	15	DB, PC, R, PG	Europe	242	469
156	24 wks	SB, Pbo	15	DB, PC, R, PG	N America	407	418
COPD CARDIOLOGY SAFETY STUDY							
168	12 wks	SB, Pbo	15	DB, PC, R, PG	US	**94**	**188**
COPD DOSE RANGING STUDIES					**totals =**	**181**	**467**
032	6 wks	SB, Pbo	5, 10, 15	DB, PC, R, PG	Europe	106	318
038	4 wks	SB, Pbo	2.5, 5	DB, PC, R, PG	N America	75	149
COPD MECHANISM OF ACTION STUDIES					**totals =**	**141**	**139**
076	12 wks	SB, Pbo	15	DB, PC, R, PG	Europe	30	29
110	12 wks	SB, Pbo	15	DB, PC, R, PG	N America	34	31
111	12 wks	SB, Pbo	15	DB, PC, R, PG	N America[e]	77	79
COPD LONG-TERM OPEN-LABEL EXTENSION STUDIES					**totals =**		**1069**
040	LTE	SB	15	Open	Europe[c]	n/a	714
041	LTE	SB	15	Open	N America[b]	n/a	355
ASTHMA CONTROLLED STUDIES					**totals =**	**295**	**764**
005	6 wks	SB, Pbo	5, 10, 15	DB, PC, R, PG	Europe, S Africa	72	231
007	4 wks	SB, Pbo	5, 10, 15	DB, PC, R, PG	Europe	99	303
022	4 wks	SB, Pbo	15	DB, PC, R, PG	Europe, S Africa	71	72
077	LTE	SB, Pbo	10, 15	DB, PC, R, PG	Europe, S Africa	53	158
ONGOING AND OTHER STUDIES							
008	2 wks	SB, Pbo	10	DB, PC, R, XO	N America	**27**[f]	**27**[f]
075	6 wks	SB	5, 10, 15	Open, R, PG	Japan	n/a	70
107	24 wks	SB, Pbo	10, 15	DB, PC, R, XO	Japan	n/a	n/a
122	28 wks	SB	10, 15	Open, R, PG	Japan	n/a	n/a
150	5 days	SB, Pbo, AZ	15	DB, PC, R, XO	Europe	n/a	n/a
157	52 wks	SB, Pbo	15	DB, PC, R, XO	Euope[c]	n/a	n/a
165	SD	SB	30, 35	O, R, XO	Europe	n/a	n/a
167	1 wk	SB	15, 30, 35	O, R, XO	Europe	n/a	n/a
					Grand Totals =	**1829**	**4446**

[b] = includes sites in Mexico
[c] = includes sites in Australia, New Zealand & S Africa
[d] = safety data from 169 not integrated
[e] = includes sites in Australia
[f] = 3-treatment crossover

DB = Double-Blind
PC = Placebo-Controlled
R = Randomized
PG = Parallel Group
XO = Cross-Over
AZ = Azithromycin

SB = SB 207499
Pbo = Placebo
O = Open
SD = single dose

LTE = Long Term Extension
mg = milligrams
bid = *bis in deum* (twice daily)

In round numbers, over 6000 patients have participated in SB 207499 COPD and asthma, controlled and uncontrolled trials. Over 4400 patients have been exposed to SB 207499, 2119 COPD patients in controlled trials, 1069 COPD patients in uncontrolled

trials and 764 asthma patients in controlled trials. The vast majority of these patients received a dose of 15 mg given twice daily.

II.B. ALL CONTROLLED TRIALS

II.B.1. DEMOGRAPHICS

The demographic characteristics of patients in all controlled studies are reflective of the inclusion/exclusion criteria of the studies and were generally similar across all SB 207499 treatment groups and placebo. Differences noted across treatment groups can be at least partially attributed to the fact that this study grouping integrates data across studies of two different conditions (i.e., asthma and COPD). Overall, the mean age of all patients treated with SB 207499 was 59.4 years, which was similar to the mean age (61.0 years) of the placebo-treated patients. The majority of the SB 207499-treated (67.4%) and placebo-treated (68.2%) were male, and the great majority of all SB 207499-treated (96.1%) and placebo-treated (96.2%) patients were Caucasian. Finally, the mean body weight for SB 207499-treated patients was 75.8kg, which was comparable to the mean body weight (76.1kg) of the placebo-treated patients. Across all controlled studies, 45.3% and 50.3% of SB 207499- and placebo-treated patients, respectively, were previous smokers, and 30.8% and 34.0% of SB 207499-treated and placebo-treated patients were current smokers, respectively. Smoking history, characterized by pack years, was similar between SB 207499-treated (48.0 pack years) and placebo-treated (49.8 pack years) patients.

With regard to pulmonary function characteristics at Screening, mean $FEV_{1.0}$ and percent predicted $FEV_{1.0}$ for patients treated with SB 207499 were 1.62L and 53.2% percent predicted, respectively. These values were similar to the mean $FEV_{1.0}$ and percent predicted $FEV_{1.0}$ for patients treated with placebo (1.60L and 52.7%, respectively) [clinstat\iss\iss.pdf:144, 1/24/03 update\120 day safety update.pdf:43-4].

NDA #21573 (12/24/02, N-000) ISS: KEY DEMOGRAPHIC AND PULMONARY CHARACTERISTICS AT SCREENING FOR COPD AND ASTHMA PATIENTS IN ALL CONTROLLED STUDIES, THE SAFETY POPULATION [clinstat\iss\iss.pdf:146, 3260, 3269, 3278, 1/24/03 update\120 day safety update.pdf:43-4]√

Demographic Characteristics	Treatments					
	Placebo	SB 207499				
	0 mg bid (N = 1802) n (%)	2.5 mg bid (N = 72) n (%)	5 mg bid (N = 366) n (%)	10 mg bid (N = 437) n (%)	15 mg bid (N = 2475) n (%)	Total SB (N = 3350) n (%)
SEX						
female	573 (31.8)	36 (50.0)	131 (35.8)	169 (38.7)	755 (30.5)	1091 (32.6)
male	1229 (68.2)	36 (50.0)	235 (64.2)	268 (61.3)	1720 (69.5)	2259 (67.4)
RACE						
white	1734 (96.2)	70 (97.2)	356 (97.3)	421 (96.3)	2373 (95.9)	3220 (96.1)
black	45 (2.5)	1 (1.4)	6 (1.6)	8 (1.8)	63 (2.5)	78 (2.3)
other[a]	23 (1.3)	1 (1.4)	4 (1.1)	8 (1.8)	39 (1.6)	52 (1.6)
AGE (years)						
< 65	990 (54.9)	30 (41.7)	257 (70.2)	365 (83.5)	1279 (51.7)	1931 (57.6)
≥ 65	812 (45.1)	42 (58.3)	109 (29.8)	72 (16.5)	1196 (48.3)	1419 (42.4)

NDA #21573 (12/24/02, N-000) ISS: KEY DEMOGRAPHIC AND PULMONARY CHARACTERISTICS AT SCREENING FOR COPD AND ASTHMA PATIENTS IN ALL CONTROLLED STUDIES, THE SAFETY POPULATION [clinstat\iss\iss.pdf:146, 3260, 3269, 3278, 1/24/03 update\120 day safety update.pdf:43-4]√

Demographic Characteristics	Treatments					
	Placebo	SB 207499				
	0 mg bid (N = 1802) n (%)	2.5 mg bid (N = 72) n (%)	5 mg bid (N = 366) n (%)	10 mg bid (N = 437) n (%)	15 mg bid (N = 2475) n (%)	Total SB (N = 3350) n (%)
mean (SD)	61.0 (12.2)	64.0 (10.0)	53.8 (15.5)	48.4 (14.8)	62.0 (11.4)	59.4 (13.3)
range	18 - 84	43 - 79	17 - 80	19 - 79	18 - 82	17 - 82
WEIGHT (kg)						
mean (SD)	76.1 (16.9)	80.0 (25.8)	75.7 (15.7)	74.7 (14.4)	75.9 (16.6)	75.8 (16.5)
range	34.0 - 181.8	38.2 - 196.0	41.0 - 139.1	30.0 - 135.0	34.5 - 147.4	30.0 - 196.0
SMOKING STATUS[b]						
current	601 (34.0)	35 (48.6)	33 (9.0)	0	936 (37.8)	1004 (30.8)
previous	890 (50.3)	37 (51.4)	103 (28.1)	71 (20.8)	1262 (51.0)	1473 (45.3)
unknown	106 (6.0)	0	109 (29.8)	102 (29.8)	107 (4.3)	318 (9.8)
PFTs & SMOKING	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
$FEV_{1.0}$	1.60 (0.61)	1.30 (0.46)	1.80 (0.72)	2.05 (0.68)	1.53 (0.56)	1.62 (0.62)
% pred. $FEV_{1.0}$	52.7 (13.41)	47.7 (12.52)	55.4 (14.31)	61.3 (12.87)	51.6 (12.77)	53.2 (13.40)
pack-years	49.8 (29.8)	55.2 (25.0)	36.6 (25.9)	31.0 (27.9)	50.2 (29.0)	48.0 (29.2)

bid = *bis in deum* (twice daily)

[a] = This category includes Asian, Hispanic, Oriental and other races.

[b] = Since the all controlled studies grouping includes non-smoking patients enrolled into the asthma studies, the Smoking Status column does not necessarily sum to 100%.

II.B.2. DISPOSITION

Subject accountability data, including reasons for study withdrawal, for all controlled studies are summarized in the table that follows. A total of 781 of 3350 SB 207499-treated (23.3%) and 343 of 1802 placebo-treated patients (19.0%) were withdrawn from the controlled studies.

The percentage of patients withdrawn from the SB 207499 (15mg twice daily) treatment group was greater (25.9% of 2475 patients) than the other SB 207499 treatment groups (6.9% of 72, 12.8% of 366, and 20.4% of 437 patients in 2.5mg, 5mg, and 10mg SB 207499 groups, respectively). In fact, the total patients withdrawn show dose-ordering with higher doses associated with greater percentages of withdrawals. The most frequently reported reason for withdrawal from all controlled studies was adverse experience. The percentage of patients withdrawn from all controlled studies for reasons other than adverse experience was comparable between SB 207499 (9.5%) and placebo (9.7%) treatment groups [clinstat\iss\iss.pdf:153, 1/24/03 update\120 day safety update.pdf:48].

NDA #21573 (12/24/02, N-000) ISS: SUMMARY OF PATIENT ACCOUNTABILITY FOR COPD AND ASTHMA PATIENTS IN ALL CONTROLLED STUDIES, THE SAFETY POPULATION [clinstat\iss\iss.pdf:154, 3498, 1/24/03 update\120 day safety update.pdf:48]√

Reason For Withdrawal	Treatments					
	Placebo	SB 207499				
	0 mg bid (N = 1802) n (%)	2.5 mg bid (N = 72) n (%)	5 mg bid (N = 366) n (%)	10 mg bid (N = 437) n (%)	15 mg bid (N = 2475) n (%)	Total SB (N = 3350) n (%)
adverse event[a]	169 (9.4)	3 (4.2)	25 (6.8)	32 (7.3)	403 (16.3)	463 (13.8)
COPD exacerbation[b]	51 (2.8)	1 (1.4)	2 (0.5)	0	50 (2.0)	53 (1.6)
not due to COPD exacerbation	118 (6.5)	2 (2.8)	23 (6.3)	32 (7.3)	353 (14.3)	410 (12.2)
insufficient efficacy	17 (0.9)	0	0	2 (0.5)	23 (0.9)	25 (0.7)
protocol deviation[c]	55 (3.1)	1 (1.4)	13 (3.6)	20 (4.6)	64 (2.6)	98 (2.9)
lost to follow-up	38 (2.1)	0	5 (1.4)	10 (2.3)	45 (1.8)	60 (1.8)
other	64 (3.6)	1 (1.4)	4 (1.1)	25 (5.7)	105 (4.2)	135 (4.0)
total withdrawn	343 (19.0)	5 (6.9)	47 (12.8)	89 (20.4)	640 (25.9)	781 (23.3)
completed study	1459 (81.0)	67 (93.1)	319 (87.2)	347 (79.4)	1835 (74.1)	2568 (76.7)

bid = *bis in deum* (twice daily)

[a] = This row includes patients withdrawn due to COPD exacerbations.

[b] = Does not apply for patients enrolled into the asthma studies.

[c] = This row includes those who were withdrawn for non-compliance.

II.B.3. EXTENT OF EXPOSURE

Of the SB 207499-treated patients in all controlled studies, most (73.8%) were treated with a dose of 15mg bid. The mean duration of exposure for patients treated with SB 207499 15mg bid was 115.1 days; (57.6%) were treated with SB 207499 15mg bid for 90 days. In comparison, mean duration of exposure for SB 207499 2.5mg bid (27.2 days) and SB 207499 5mg bid (33.6 days) was far less, and reflected that these doses were employed in Phase II dose-ranging studies of shorter duration (4 to 6 weeks) [clinstat\iss\iss.pdf:161, 1/24/03 120 day safety update.pdf:50].

Our usual criteria for the minimum amount of safety data is either 200 patients exposed for one year or 300 patients exposed for six months and 100 exposed for one year. Though these data reflect the fact that neither criteria was met at the time of submission of the 120 day safety update by the controlled trial data, the addition of the uncontrolled trial data in the ISS far exceed these minimum criteria [clinstat\iss\iss.pdf:347].

NDA #21573 (12/24/02, N-000) ISS: DURATION OF EXPOSURE FOR COPD AND ASTHMA PATIENTS IN ALL CONTROLLED STUDIES, THE SAFETY POPULATION [clinstat\iss\iss.pdf:160, 3507, 3516, 1/24/03 update\120 day safety update.pdf:50]√

Exposure[a] (days)	Treatments					
	Placebo	SB 207499				
	0 mg bid (N = 1802) n (%)	2.5 mg bid (N = 72) n (%)	5 mg bid (N = 366) n (%)	10 mg bid (N = 437) n (%)	15 mg bid (N = 2475) n (%)	Total SB (N = 3350) n (%)
1	1802 (100.0)	72 (100.0)	366 (100.0)	437 (100.0)	2475 (100.0)	3350 (100.0)
> 1	1792 (99.4)	71 (98.6)	363 (99.2)	431 (98.6)	2450 (99.0)	3315 (99.0)

NDA #21573 (12/24/02, N-000) ISS: DURATION OF EXPOSURE FOR COPD AND ASTHMA PATIENTS IN ALL CONTROLLED STUDIES, THE SAFETY POPULATION [clinstat\iss\iss.pdf:160, 3507, 3516, 1/24/03 update\120 day safety update.pdf:50]√

Exposure[a] (days)	Treatments						
	Placebo	SB 207499					
	0 mg bid (N = 1802) n (%)	2.5 mg bid (N = 72) n (%)	5 mg bid (N = 366) n (%)	10 mg bid (N = 437) n (%)	15 mg bid (N = 2475) n (%)	Total SB (N = 3350) n (%)	
≥ 14	1725 (95.7)	70 (97.2)	345 (94.3)	414 (94.7)	2264 (91.5)	3093 (92.3)	
≥ 28	1623 (90.1)	52 (72.2)	313 (85.5)	387 (88.6)	2128 (86.0)	2880 (86.0)	
≥ 60	1197 (66.4)	0	2 (0.5)	141 (32.3)	1697 (68.6)	1840 (54.9)	
≥ 90	996 (55.3)	0	0	135 (30.9)	1426 (57.6)	1561 (46.6)	
≥ 180	295 (16.4)	0	0	118 (27.0)	418 (16.9)	536 (16.0)	
≥ 360	6 (0.3)	0	0	22 (5.0)	0	22 (0.7)	
mean (SD)	115.8 (74.3)	27.2 (4.4)	33.6 (10.3)	119.9 (134.1)	115.1 (68.2)	104.9 (81.1)	
median	140	28	30	43	162	84	
range	1 - 389	1 - 34	1 - 63	1 - 378	1 - 231	1 - 378	

bid = *bis in deum* (twice daily)

[a] = Calculation of exposure: (date of last dose) - (date of first dose) + 1

II.B.4. ADVERSE EVENTS (AES)

The numbers (%) of patients reporting on-therapy AEs, irrespective of relationship to study medication, in all controlled studies are presented. The numbers (%) of these patients with the most frequently reported on-therapy AEs that were more frequent in the high-dose SB 207499 group (15 mg twice daily) than in the placebo group are summarized in the table below. In this table, AEs are listed by descending order of frequency in the Total SB 207499 group. The text and table notations incorrectly identify the referenced AE tables as being listed by descending order of frequency in the high-dose (15 mg twice daily) SB 207499 group [clinstat\iss\iss.pdf:169, 1/24/03 update\120 day safety update.pdf:56-7, 237-9].

Gastrointestinal adverse events, which are capitalized in the table, are prominent and three of the seven lead the list. Nausea, the most frequent AE in the table, shows dose-ordered frequency of occurrence.

NDA #21573 (12/24/02, N-000) ISS: NUMBER (%) OF PATIENTS WITH THE MOST FREQUENTLY REPORTED AEs WHERE THE FREQUENCY OF THAT AE IN ANY COLUMN WAS > 2.0% AND THE FREQUENCY IN THE HIGH-DOSE SB 207499 (15 mg bid) GROUP WAS GREATER THAN PLACEBO FOR COPD AND ASTHMA PATIENTS IN ALL CONTROLLED STUDIES, THE SAFETY POPULATION [clinstat\iss\iss.pdf:170, 3525-46, 1/24/03 update\120 day safety update.pdf:57, 237-9]√

Adverse Event	Treatments					
	Placebo	SB 207499				
	0 mg bid (N = 1802) n (%)	2.5 mg bid (N = 72) n (%)	5 mg bid (N = 366) n (%)	10 mg bid (N = 437) n (%)	15 mg bid (N = 2475) n (%)	Total SB (N = 3350) n (%)
TOTAL[a]	1214 (67.4)	48 (66.7)	175 (47.8)	230 (52.6)	1817 (73.4)	2270 (67.8)
NAUSEA	76 (4.2)	2 (2.8)	17 (4.6)	33 (7.6)	361 (14.6)	413 (12.3)
DIARRHEA	110 (6.1)	4 (5.6)	11 (3.0)	15 (3.4)	325 (13.1)	355 (10.6)

NDA #21573 (12/24/02, N-000) ISS: NUMBER (%) OF PATIENTS WITH THE MOST FREQUENTLY REPORTED AEs WHERE THE FREQUENCY OF THAT AE IN ANY COLUMN WAS > 2.0% AND THE FREQUENCY IN THE HIGH-DOSE SB 207499 (15 mg bid) GROUP WAS GREATER THAN PLACEBO FOR COPD AND ASTHMA PATIENTS IN ALL CONTROLLED STUDIES, THE SAFETY POPULATION [clinstat\iss\iss.pdf:170, 3525-46, 1/24/03 update\120 day safety update.pdf:57, 237-9]√

Adverse Event	Treatments					
	Placebo	SB 207499				
	0 mg bid (N = 1802) n (%)	2.5 mg bid (N = 72) n (%)	5 mg bid (N = 366) n (%)	10 mg bid (N = 437) n (%)	15 mg bid (N = 2475) n (%)	Total SB (N = 3350) n (%)
ABDOMINAL PAIN	97 (5.4)	1 (1.4)	4 (1.1)	16 (3.7)	256 (10.3)	277 (8.3)
headache	109 (6.0)	7 (9.7)	24 (6.6)	32 (7.3)	198 (8.0)	261 (7.8)
DYSPEPSIA	38 (2.1)	0	8 (2.2)	7 (1.6)	167 (6.7)	182 (5.4)
VOMITING	22 (1.2)	1 (1.4)	5 (1.4)	11 (2.5)	133 (5.4)	150 (4.5)
injury	77 (4.3)	1 (1.4)	5 (1.4)	6 (1.4)	108 (4.4)	120 (3.6)
infection viral	49 (2.7)	0	6 (1.6)	15 (3.4)	86 (3.5)	107 (3.2)
dizziness	47 (2.6)	2 (2.8)	2 (0.5)	8 (1.8)	90 (3.6)	102 (3.0)
back pain	57 (3.2)	0	5 (1.4)	4 (0.9)	90 (3.6)	99 (3.0)
insomnia	19 (1.1)	1 (1.4)	4 (1.1)	2 (0.5)	71 (2.9)	78 (2.3)
FLATULENCE	26 (1.4)	0	1 (0.3)	0	72 (2.9)	73 (2.2)
fatigue	28 (1.6)	3 (4.2)	5 (1.4)	3 (0.7)	55 (2.2)	66 (2.0)
arthralgia	27 (1.5)	1 (1.4)	3 (0.8)	0	51 (2.1)	55 (1.6)
pain	22 (1.2)	2 (2.8)	2 (0.5)	3 (0.7)	45 (1.8)	52 (1.6)
ANOREXIA	6 (0.3)	0	0	0	51 (2.1)	51 (1.5)

bid = *bis in deum* (twice daily)
[a] = Total represents total number of patients reporting at least one adverse event.

II.B.5. DEATHS

Seventeen COPD patients died during the controlled studies or during the post-therapy follow-up period. One patient died during the placebo run-in period of a suicide. Seven on-therapy, double-blind period fatal AEs occurred, one in the placebo group and six in the SB 207499 group. All of these were in patients with COPD and all were due to atherosclerotic vascular or pulmonary diseases. Nine patients died during the post-therapy period, 5 from the placebo group and 4 from the SB 207499 group. Seven of these post-therapy deaths were due to atherosclerotic vascular disease and one was attributed to an exacerbation of COPD. The investigators judged all the fatal AEs "not related" or "unlikely" to be related to the study medication [clinstat\iss\iss.pdf:225, 227, 1/24/03 update\120 day safety update.pdf:80].

NDA #21573 (12/24/02, N-000) ISS: PATIENT DEATHS FOR COPD AND ASTHMA PATIENTS IN ALL CONTROLLED STUDIES, THE SAFETY POPULATION [clinstat\iss\iss.pdf:225-6, 4555-60, clinstat\168.pdf:480, 1/24/03 update\120 day safety update.pdf:80]√

Patient ID	Age (yrs)	Gender	Days On/After[a]	Cause	Fatal SAE[b]	Related
RUN-IN - PLACEBO						
168.648.22928	72	M	12/0	self-inflicted gun shot	suicide	Not
ON-THERAPY - PLACEBO						
039.212.05091	75	F	157/0	MI	cardiac failure MI coronary thrombosis	Not Not Not
ON-THERAPY - SB 207499 (15 mg twice daily)						

NDA #21573 (12/24/02, N-000) ISS: PATIENT DEATHS FOR COPD AND ASTHMA PATIENTS IN ALL CONTROLLED STUDIES, THE SAFETY POPULATION [clinstat\iss\iss.pdf:225-6, 4555-60, clinstat\168.pdf:480, 1/24/03 update\120 day safety update.pdf:80]√

Patient ID	Age (yrs)	Gender	Days On/After[a]	Cause	Fatal SAE[b]	Related
032.083.50490	63	M	32/0	coronary insufficiency, KHK[c]	MI	Unlikely
039.206.06193	73	M	151/0	possible MI per coroner	MI	Not
042.243.07614	71	F	72/1	MI, CHF	MI	Unlikely
091.039.10022	67	M	148/0	AAA[d]	aneursym constipation	Not Unlikely
091.146.10719	72	M	174/1	cerebral aneurysm rupture	aneurysm	Unlikely
111.020.13504	70	M	33/0	stroke	cerebrovascular disorder	Unlikely
POST-THERAPY - PLACEBO						
032.083.50335	74	M	50/11	cardiovascular collapse	cardiac failure respiratory disorder	Unlikely Unlikely
039.006.05531	75	M	137/5	CHF	cardiac failure	Unlikely
042.201.08584	77	M	9/2	ruptured aortic aneurysm	aneurysm	Unlikely
042.338.14323	58	M	193/64	heart failure	cardiac failure	Unlikely
042.291.07201	57	F	27/5	natural causes	MI	Unlikely
POST-THERAPY - SB 207499 (15 mg twice daily)						
039.007.05548	63	M	172/23	MI (ischemic cardiomyopathy)	myocardial ischemia	Unlikely
042.221.14165	79	M	26/19	COPD exacerbation, respiratory insufficiency	chronic obstructive airways disease, respiratory insufficiency	Not Not
091.148.10880	80	M	128/7	cardio-respiratory uncompensation	cardiac failure	Not
111.027.12319	74	F	53/2	MI	MI	Not

[a] = days on randomized medication/days post study
[b] = preferred term
[c] = coronary artery disease
[d] = abdominal aortic aneurysm

II.B.6. SERIOUS ADVERSE EVENTS (SAES)

The numbers of patients treated with doses of SB 207499 lower than 15mg twice daily and reporting SAEs (16 patients treated with the three lowest doses) were too small to allow comparisons of SAE patterns across SB 207499 doses. Total SAEs were less frequent in the highest-dose SB 207499 group than in the placebo group. The table focuses on those SAEs that were more frequent in the high-dose SB 207499 group than in the placebo group. All SAEs that fit this criterion have a frequency of much less than 1% yielded by very small numbers of patients for each SAE and have no apparent unifying theme [clinstat\iss\iss.pdf:228-30].

NDA #21573 (12/24/02, N-000) ISS: NUMBER (%) OF PATIENTS WITH THE MOST FREQUENTLY (≥ 2 PATIENTS IN ANY TREATMENT GROUP) REPORTED SAEs WHERE THE FREQUENCY OF THAT SAE IN THE SB 15 mg BID COLUMN WAS GREATER THAN PLACEBO FOR COPD AND ASTHMA PATIENTS IN ALL CONTROLLED STUDIES, THE SAFETY POPULATION [clinstat\iss\iss.pdf:228-9, 4572-7, 1/24/03 update\120 day safety update.pdf:81-2]√

Serious Adverse Event	Treatments					
	Placebo	SB 207499				
	0 mg bid (N = 1802) n (%)	2.5 mg bid (N = 72) n (%)	5 mg bid (N = 366) n (%)	10 mg bid (N = 437) n (%)	15 mg bid (N = 2475) n (%)	Total SB (N = 3350) n (%)
TOTAL[a]	110 (6.1)	1 (1.4)	7 (1.9)	8 (1.8)	127 (5.1)	143 (4.3)
cerebrovascular disorder	1 (0.1)	0	0	0	6 (0.2)	6 (0.2)
aneurysm	2 (0.1)	0	0	0	5 (0.2)	5 (0.1)
abdominal pain	0	0	0	0	4 (0.2)	4 (0.1)
vascular disorder	1 (0.1)	0	0	0	4 (0.2)	4 (0.1)
urinary retention	0	0	0	0	3 (0.1)	3 (0.1)
alcohol intolerance	0	0	0	0	2 (0.1)	2 (0.1)
myalgia	0	0	0	0	2 (0.1)	2 (0.1)

bid = *bis in deum* (twice daily)

[a] = Total represents total number of patients reporting at least one serious adverse event.

II.B.7. WITHDRAWALS DUE TO ADVERSE EVENTS

The numbers (%) of patients with adverse experiences leading to withdrawal from all controlled studies in COPD and asthma patients are presented for those AEs leading to the withdrawal of five or more patients in the SB 207499 15mg twice daily treatment group. These are summarized in the table that follows [clinstat\iss\iss.pdf:238-40, 1/24/03 update\120 day safety update.pdf:87]. The five most frequent reasons for withdrawal due to an AE were the gastrointestinal complaints of nausea, abdominal pain, diarrhea, vomiting and dyspepsia.

NDA #21573 (12/24/02, N-000) ISS: NUMBER (%) OF PATIENTS WITH THE MOST FREQUENTLY (≥ 5 PATIENTS IN THE 15 mg TWICE DAILY TREATMENT GROUP) REPORTED AEs LEADING TO WITHDRAWAL WHERE THE FREQUENCY OF THAT SAE IN THE SB 15 mg TWICE DAILY COLUMN WAS GREATER THAN PLACEBO FOR COPD AND ASTHMA PATIENTS IN ALL CONTROLLED STUDIES, THE SAFETY POPULATION [clinstat\iss\iss.pdf:239, 4765-72, 1/24/03 update\120 day safety update.pdf:87]√

Adverse Event Leading To Withdrawal	Treatments					
	Placebo	SB 207499				
	0 mg bid (N = 1802) n (%)	2.5 mg bid (N = 72) n (%)	5 mg bid (N = 366) n (%)	10 mg bid (N = 437) n (%)	15 mg bid (N = 2475) n (%)	Total SB (N = 3350) n (%)
TOTAL[a]	161 (8.9)	3 (4.2)	25 (6.8)	31 (7.1)	388 (15.7)	447 (13.3)
nausea	8 (0.4)	0	0	8 (1.8)	114 (4.6)	122 (3.6)
abdominal pain	9 (0.5)	0	2 (0.5)	3 (0.7)	89 (3.6)	94 (2.8)
diarrhea	7 (0.4)	0	1 (0.3)	4 (0.9)	82 (3.3)	87 (2.6)
vomiting	3 (0.2)	0	0	3 (0.7)	32 (1.3)	35 (1.0)
dyspepsia	2 (0.1)	0	0	1 (0.2)	25 (1.0)	26 (0.8)
dizziness	2 (0.1)	0	0	2 (0.5)	21 (0.8)	23 (0.7)
headache	2 (0.1)	0	0	1 (0.2)	19 (0.8)	20 (0.6)
anorexia	0	0	0	0	10 (0.4)	10 (0.3)
flatulence	1 (0.1)	0	0	0	10 (0.4)	10 (0.3)
melena	1 (0.1)	0	0	0	10 (0.4)	10 (0.3)
insomnia	0	0	0	0	7 (0.3)	7 (0.2)

NDA #21573 (12/24/02, N-000) ISS: NUMBER (%) OF PATIENTS WITH THE MOST FREQUENTLY (≥ 5 PATIENTS IN THE 15 mg TWICE DAILY TREATMENT GROUP) REPORTED AEs LEADING TO WITHDRAWAL WHERE THE FREQUENCY OF THAT SAE IN THE SB 15 mg TWICE DAILY COLUMN WAS GREATER THAN PLACEBO FOR COPD AND ASTHMA PATIENTS IN ALL CONTROLLED STUDIES, THE SAFETY POPULATION
[clinstat\iss\iss.pdf:239, 4765-72, 1/24/03 update\120 day safety update.pdf:87]√

Adverse Event Leading To Withdrawal	Treatments					
	Placebo	SB 207499				
	0 mg bid (N = 1802) n (%)	2.5 mg bid (N = 72) n (%)	5 mg bid (N = 366) n (%)	10 mg bid (N = 437) n (%)	15 mg bid (N = 2475) n (%)	Total SB (N = 3350) n (%)
fatigue	0	0	0	0	6 (0.2)	6 (0.2)
asthenia	2 (0.1)	0	0	1 (0.2)	5 (0.2)	6 (0.2)
constipation	0	0	0	0	5 (0.2)	5 (0.1)
malaise	1 (0.1)	0	0	0	5 (0.2)	5 (0.1)

bid = *bis in deum* (twice daily)
[a] = Total represents total number of patients withdrawn due to an adverse event.

II.B.8. GASTROINTESTINAL ADVERSE EVENTS OF CONCERN

II.B.8.a. RATIONALE FOR THIS CATEGORIZATION

The concept of GIAE of concern was to single out these cases for thorough evaluation. The mesenteric arteritis seen in primates during the earliest pre-clinical studies is a largely unmonitorable adverse event. In order to find a path forward for the possible approval of this drug, we devised this plan to evaluate one of the only not-immediately-fatal, possibly-monitorable consequences of mesenteric arteritis, ischemic colitis. Our intent was to monitor FOB and orthostatic changes, within a short time after the event and daily until resolution. The FOB was to signal the need for a colonoscopy and the orthostatic changes were to alert the investigator to possible acute volume depletion that might signal frank bowel infarction.

Both of these measures represented hope more than knowledge. Our feeling was that rigorous evaluation of the colon is widely supported as a routine surveillance method to identify adenomas/adenocarcinomas of the colon in patients over the age of 50 years. The use of colonoscopy for cancer surveillance is recommended as a routine measure by many professional societies and organizations. We felt that melena, bright red blood *per rectum* or a positive FOB in a patient population of this age would certainly be adequate justification for a colon evaluation under normal clinical conditions and would represent "usual care." Our choice of colonoscopy as the suggested evaluation of choice is based on a prior drug that caused ischemic colitis and generated discrete areas of mucosal atrophy, primarily in the transverse colon. We felt that rigorous evaluation of the colon showing no such changes in a large number of patients might provide indirect reassurance of the absence of mesenteric arteritis.

II.B.8.b. IMPLEMENTATION

Clinical studies in which GIAEs of concern were scheduled to be recorded, if present, included all Phase III studies of COPD patients (Studies 039, 042, 076, 091, 110, 111, 156, 168). GIAEs of concern and FOBs were not recorded in the Phase II dose-ranging studies of patients with COPD (Studies 032 and 038) or in the Phase III studies of patients with asthma (Studies 005, 007, 022 and 077). GIAEs were also recorded in the uncontrolled long-term Phase III studies of COPD patients (Studies 040 and 041). The analysis of GIAEs of concern in the long-term studies is presented in the Long-Term Treatment Effect, Uncontrolled Trials section of this review and reported under the All Uncontrolled Trials section of this review.

Investigators identified gastrointestinal adverse events (GIAEs) of concern based on reports from patients of GI symptoms (e.g., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhea, or vomiting) that caused the patient to be concerned or interfered with their activities (including eating and sleeping). The investigator was to complete a clinical assessment of each such GI symptom reported within 24 hours of its occurrence. When a GI symptom of concern to the patient was reported, the patient was asked to use a previously provided FOB (fecal occult blood) test kit and to schedule a clinic visit within 24 hours. Failure to provide a FOB specimen was to trigger a rectal examination with FOB testing at the first clinic visit. At the visit, appropriate physical and laboratory assessments were conducted and the returned FOB test kit was examined. If the kit was not used and/or not provided at the visit, a fecal sample for evaluation of FOB was to be obtained by digital rectal examination. Assessments of FOB, complete blood count, and orthostatic changes in blood pressure were to be continued until the GIAE of concern resolved [clinstat\iss\iss.pdf:166, 198, clinstat\168:1102-5, 1/31/03 clinstat\168.pdf:1102-5].

The actual protocol-specified directions to clinical investigators were compared for all controlled and uncontrolled trials and are presented in the following table. Daily follow-up of GIAEs of concern was encouraged by this Agency but was mandated in only five of the eight controlled Phase 3 trials and in only one of the two Phase 3 uncontrolled trials by the sponsor. The remaining four trials left follow-up specifics and frequency to the discretion of the Clinical Investigator. In Studies 041, 156 and 168, if the FOB test was positive or if the patient reported melena during the treatment phase, the patient was to be referred to a gastroenterologist for a complete colonoscopy as soon as possible. This requirement was added to all three protocols by amendment after they had begun at the request of the FDA because we feared that insufficient safety data was being obtained specifically to evaluate colonic pathology as an etiology of the frequent gastrointestinal complaints associated with SB 207499 [clinstat\039.pdf:2044-5, 2126-30, clinstat\040.pdf:2277-9, clinstat\041.pdf:1, 95, 1747, 1861-6, 4407, clinstat\042.pdf:1771-2, clinstat\076.pdf:627, 681-2, clinstat\091.pdf:2178-80, clinstat\110.pdf:572, 623-7, clinstat\111.pdf:795, 848-52, clinstat\156.pdf:1, 159, 1557, 1718-22, clinstat\168.pdf:1, 154, 964, 1102-5, 1/24/03 update\120 day safety update.pdf:158].

NDA #21573 (12/24/02, N-000) ISS: PROTOCOL-SPECIFIED DIRECTIONS ABOUT HANDLING GIAEs OF CONCERN FOR CLINICAL INVESTIGATORS COMPARED FOR ALL CONTROLLED AND UNCONTROLLED TRIALS [clinstat\039.pdf:2044-5, 2126-30, clinstat\040.pdf:2277-9, clinstat\041.pdf:1861-6, 4407, clinstat\042.pdf:1771-2, clinstat\076.pdf:627, 681-2, clinstat\091.pdf:2178-80, clinstat\110.pdf:572, 623-7, clinstat\111.pdf:795, 848-52, clinstat\156.pdf:1718-22, clinstat\168.pdf:1102-5, 1/24/03 update\120 day safety update.pdf:158]√

	Controlled								Uncontrolled	
	Pivotal				CV[a]	Mechanism			LTE[b]	
	039	042	091	156	168	076	110	111	040	041
FIRST VISIT WITH CI[c]										
seen within 24 hours	X	X	X	X	X	X	X	X	X	X
FOB[d]	X	X	X	X	X	X	X	X	X	X
orthostatic VS[e]	X	X	X	X	X	X	X	X	X	X
FOLLOW-UP FREQUENCY										
daily	X			X	X		X	X		X
discretionary		X	X			X			X	
FOLLOW-UP STUDIES										
FOB[d]	X			X	X		X	X		X
orthostatic VS[e]	X			X	X		X	X		X
discretionary		X	X			X			X	
COLONOSCOPY										
mandated for melena or FOB[d] +				X	X					X
emphasizes transverse colon				X	X					X
CRF										
FOB[d]	X	X	X	X	X	X	X	X	X	X
orthostatic VS[e]	X	X	X	X	X	X	X	X	X	X
mentions GIAEs[f] of concern	X	X	X	X	X	X	X	X	X	X

[a] = CardioVascular Study [b] = Long Term Extension [c] = Clinical Investigator
[d] = Fecal Occult Blood [e] = Vital Signs [f] = Gastrointestinal Adverse Events

The numbers (%) of patients with the most frequently reported on-therapy GIAEs of concern in the Phase III studies, as defined by occurring in ≥ 0.5% of patients in either treatment group (SB 207499 or placebo), are summarized in the table that follows. Overall, about a three-times higher frequency of GIAEs of concern (as a percent of the total number exposed to that treatment) were reported in patients treated with SB 207499, 15 mg twice daily, (12.5%) as were reported in patients treated with placebo (4.2%). A greater frequency in the SB 207499 treatment group was apparent for every one of the most frequently reported GIAEs in the table [clinstat\iss\iss.pdf:198-9, 1/24/03 update\120 day safety update.pdf:69]:

NDA #21573 (12/24/02, N-000) ISS: NUMBER (%) OF PATIENTS WITH MOST FREQUENTLY (≥ 0.5% OF PATIENTS IN EITHER TREATMENT GROUP) REPORTED GASTROINTESTINAL ADVERSE EVENTS OF CONCERN IN PHASE 3 STUDIES [clinstat\iss\iss.pdf:199, 4256-8, 1/24/03 update\120 day safety update.pdf:69. 423-5]√

Adverse Event (preferred term)	Treatment Group	
	Placebo (N = 1326) n (%)	SB 207499 15 mg twice daily (N = 2119) n (%)
Total[a]	56 (4.2)	264 (12.5)
abdominal pain	30 (2.3)	119 (5.6)
diarrhea	23 (1.7)	108 (5.1)
nausea	8 (0.6)	90 (4.2)

NDA #21573 (12/24/02, N-000) ISS: NUMBER (%) OF PATIENTS WITH MOST FREQUENTLY (≥ 0.5% OF PATIENTS IN EITHER TREATMENT GROUP) REPORTED GASTROINTESTINAL ADVERSE EVENTS OF CONCERN IN PHASE 3 STUDIES [clinstat\iss\iss.pdf:199, 4256-8, 1/24/03 update\120 day safety update.pdf:69. 423-5]√		
Adverse Event (preferred term)	Treatment Group	
	Placebo (N = 1326) n (%)	SB 207499 15 mg twice daily (N = 2119) n (%)
vomiting	6 (0.5)	60 (2.8)
dyspepsia	4 (0.3)	34 (1.6)
melena	9 (0.7)	21 (1.0)
flatulence	2 (0.2)	18 (0.8)
gastroesophageal reflux	0	10 (0.5)
[a] = Total represents total number of patients reporting at least one GIAE of concern. Data sources came from studies 039, 042, 091, 156, 076, 110, 111 and 168.		

In addition, a little less than twice the frequency of patients treated with SB 207499 who reported GIAEs of concern pre-therapy and on-therapy were considered related to the treatment (76.9%) compared with placebo (44.6%) [clinstat\iss\iss.pdf:199, 1/24/03 update\120 day safety update.pdf:70].

A total of 154 (58%) of the 264 patients treated with SB 207499 15 mg twice daily who reported one or more GIAEs of concern also had accompanying FOB tests performed within 14 days of reporting a GIAE of concern. Of these 154 patients, 15 (9.7%) of patients had a positive test result. A total of 31 (55%) of the 56 placebo-treated patients who reported at least one GIAE of concern also had accompanying FOB tests performed within 14 days of reporting a GIAE of concern; 6 (19.4%) of 31 patients tested positive for fecal occult blood [1/24/03 update\120 day safety update.pdf:70]. This failure to follow up GIAEs of concern with timely FOB testing represents quite a departure from both the protocols and the rigor that we expected would be brought to bear on this subset of patients.

NDA #21573 (12/24/02, N-000) ISS: NUMBER (%) OF PATIENTS WITH MOST FREQUENTLY (≥ 0.5% OF PATIENTS IN EITHER TREATMENT GROUP) REPORTED GASTROINTESTINAL ADVERSE EVENTS OF CONCERN IN PHASE 3 STUDIES [clinstat\iss\iss.pdf:199, 4256-8, 1/24/03 update\120 day safety update.pdf:69. 423-5, 432-3]√			
Characteristic	Placebo	SB 207499	Total
GIAE of concern	56	264	320
FOB within 14 days of GIAE of concern	31	154	185
FOB positive	6	15	21
GIAE = GastroIntestinal Adverse Event FOB = Fecal Occult Blood			

At this point the NDA encourages the reviewer to locate the patients in the Phase 3 studies with positive FOB results within two weeks of a GIAE of concern and the colonoscopy results in a series of SAS transport file datasets [clinstat\iss\iss.pdf:200, 1/24/03 update\120 day safety update.pdf:68].

A total of 157 (59%) patients treated with SB 207499 15 mg twice daily who reported one or more GIAEs of concern and 42 (75%) patients treated with placebo who

reported one or more GIAEs of concern also had accompanying orthostatic vital sign changes of concern (i.e., systolic and diastolic blood pressures and heart rate) evaluation [1/24/03 update\120 day safety update.pdf:70]. From patient details in the eight individual studies, these large signals did not excite much interest on the part of the investigators who treated them as experimental data points devoid of clinical utility [clinstat\039.pdf:167-73, clinstat\042.pdf:143-52, clinstat\076.pdf:110-4, 118, clinstat\091.pdf:168-75, clinstat\110.pdf:106-7, 112, 311-21, clinstat\111.pdf:173-4, clinstat\156.pdf:163-4, clinstat\168.pdf:148-51, 58].

II.B.8.c. COLONOSCOPIES

A total of 19 patients had colonoscopies performed due to events that occurred during Studies 156 and 168. Ten of these patients (4 placebo-treated and 6 SB 207499-treated patients) who had a colonoscopy performed experienced at least one GIAE of concern. Only four of these ten colonoscopies were carried out within four weeks (Colonoscopy Day - Onset Day, in the next table) after the GIAE of concern and only two colonoscopies were performed within two weeks of the signal event.

A total of 6 patients with AEs in the GI body system that were not considered GIAEs of concern had colonoscopies performed, including 2 placebo-treated and 4 SB 207499-treated patients. A total of 3 patients with gastrointestinal symptoms that were not reported as adverse events had colonoscopies performed (2 placebo-treated and 1 SB 207499-treated patient). Brief summaries of the colonoscopy patients in both the placebo and SB 207499 treatment groups are provided below [1/24/02 update\120 day safety update.pdf:71-2].

NDA #21573 (12/24/02, N-000) ISS: PATIENTS WITH COLONOSCOPIES IN STUDIES 156 & 168 [1/24/03 update\120 day safety update.pdf:72]√					
Patient Number	**Age (years)**	**Colonoscopy Day**	**GI Symptoms**	**Onset Day**	**FOB Results**
Placebo			**GIAE OF CONCERN**		
156.420.16592	72	51	hemorrhage rectum	11	negative
			diarrhea	15	negative
			hemorrhage rectum	40	negative
156.457.14400	61	256	melena	182	positive
156.515.14954	70	176	diverticulitis	175	not done
			hemorrhoids	175	not done
168.625.18447	68	105	abdominal pain	70	positive
SB 207499					
156.490.16423	69	177	hemorrhoids	134	positive
156.505.15358	76	86	abdominal pain	66	positive
			vascular disorder	66	positive
156.509.22706	65	32	abdominal pain	1	positive
			nausea	1	positive
			melena	2	positive
			dizziness	4	positive
156.526.15369	67	77	hemorrhage rectum	72	not done
168.611.18097	73	31	gastritis	6	negative

NDA #21573 (12/24/02, N-000) ISS: PATIENTS WITH COLONOSCOPIES IN STUDIES 156 & 168 [1/24/03 update\120 day safety update.pdf:72]√					
Patient Number	**Age (years)**	**Colonoscopy Day**	**GI Symptoms**	**Onset Day**	**FOB Results**
168.648.18699	69	162	colitis	53	positive
ADVERSE EVENTS IN THE GASTROINTESTINAL BODY SYSTEM					
Placebo					
156.449.16402	71	177	dyspepsia dyspepsia dyspepsia	1 16 20	negative negative negative
168.647.18582	77	76	abdominal pain	2	negative
SB 207499					
156.478.15560	65	171	diarrhea GERD diarrhea	53 61 87	negative negative negative
156.496.14728	73	135	diarrhea	2	positive
168.625.18440	52	55	neoplasm/colon polyp	54	negative
168.648.18372	57	49	diarrhea	1	negative
GASTROINTESTINAL SYMPTOMS NOT REPORTED AS AN ADVERSE EVENT					
Placebo					
156.481.14621	58	33	lower quadrant discomfort rectal bleeding	NA	negative
168.641.18060	64	38	hematochezia	NA	negative
SB 207499					
156.405.15063	70	111	GI bleeding	NA	negative

- Two additional placebo-treated patients from Study 156 had a gastrointestinal procedure performed, other than a colonoscopy, including one patient (156.468.14632) with GI symptoms that were not reported as adverse events and one patient (156.465.16099) who experienced a GIAE of concern.
- Two other patients had GIAEs of concern and colonoscopies during the Run-In period of Study 156 and are not included in this table.

II.B.8.d. EXAMINATION RESULTS IN SB 207499 PATIENTS

II.B.8.d.i. PATIENTS WITH GIAES OF CONCERN

1. Patient 156.490.16423 experienced a GIAE of concern (also reported as an SAE) of hemorrhoids on Day 134. The event was of moderate intensity, considered unlikely related to study medication, and resolved after 9 days. A colonoscopy was performed on Day 177 (27 Nov 2001). The rectum, cecum, and the ascending, transverse, and descending colon were normal and free of polyps. The sigmoid colon did not have any firm strictures or acute inflammation, yet there were extensive diverticula observed.

2. Patient 156.505.15358 experienced moderate GIAEs of concern of abdominal pain and vascular disorder (abdominal bruit to left of umbilicus) on Day 66 of treatment with SB 207499. Both events were considered not related to study medication by the Investigator and resolved after 10 days. The patient also experienced an AE of melena (positive FOB) on Day 11 that was not reported as a GIAE of concern. A colonoscopy was performed on Day 86 (22 Aug 2001) and in the cecum, just behind the ileocecal valve, a 1.5-cm diameter polyp was seen. This polyp was not removed

due to two other large masses (6- 8 cm diameter) observed at the hepatic and splenic flexures. Biopsies were taken of the two large masses and microscopic analysis revealed villotubular adenoma for the hepatic flexure mass and villotubular adenoma with severe glandular dysplasia and suspicion of submucosal invasion for the splenic flexure mass. The patient was withdrawn on Day 106 due to an AE of colon carcinoma. No other findings were noted during the colonoscopy.

3. Patient 156.509.22706 experienced GIAEs of dizziness (onset Day 4), abdominal pain (onset Day 1), nausea (onset Day 1) and melena (onset Day 2) that were considered either suspected or probably related to study medication. The patient was withdrawn on Day 5. Orthostatic changes in diastolic blood pressure reached a level of clinical concern (-10mmHg) on Day 8. FOB tests prior to baseline were positive as well as on Days 10, 12, and 13. A colonoscopy was performed Day 32 (22 Feb 2002). The cecum and ascending colon were normal. The transverse colon had a few scattered diverticula. The descending colon had a single small polyp removed by ablation. The sigmoid colon had two small polyps and the rectum had one small polyp removed by ablation. There was diverticulitis in the descending and sigmoid colon. The patient had small internal hemorrhoids, which were not actively bleeding.

4. Patient 156.526.15369 experienced a GIAE of rectal hemorrhage on Day 72 of treatment with SB 207499. FOB results during the run-in period were negative but no FOB tests were performed during the double-blind treatment period. Orthostatic changes in vital signs were likewise not assessed during the double-blind period. A colonoscopy was performed on Day 77 (02 Oct 2001) and two polyps were removed from the sigmoid and descending colon. Histology showed both polyps were tubular adenomas. Multiple diverticula were observed in the ascending and descending colon and cecum.

5. Patient 168.611.18097 had a history of chronic diarrhea and *C. difficile* colitis (treated successfully with Flagyl) and current gastrointestinal conditions of diverticulitis, dyspepsia, and esophagitis (GERD). Fecal occult blood results were negative at Baseline. On Day 6, the patient (168.611.18097) experienced gastritis, a SAE of moderate intensity requiring hospitalization that was considered unlikely related to the study drug by the Investigator. The event lasted 2 days and study drug was stopped; the patient was discontinued from the study due to the gastrointestinal SAE. A FOB test was not recorded specifically as a result of the event; however, melena was reported by the Investigator as a gastrointestinal symptom resolving on Day 8 (Appendix D Listing 9). As a result of the GIAE and melena a colonoscopy and esophagogastroduodenoscopy (EGD) was scheduled on Day 10 (25 October 2001). The patient could not endure the preparation for the colonoscopy and thus only the EGD was performed. The esophageal, stomach, and duodenal mucosa were normal. Duodenal mucosa was biopsied to rule out psilosis (sprue). Microscopic analysis revealed no pathology of the duodenal mucosa. The patient was rescheduled for a colonoscopy on Day 31 (15 November 01). Mucosa of the terminal ileum, ileocecal valve, cecum, ascending colon, and rectum was normal. Multiple diverticuli

were observed in the transverse colon, descending colon and sigmoid colon, but the areas were otherwise normal. Random biopsies were taken throughout the colon from the cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum to rule out pathologies. The pathology report showed no remarkable changes and no pathology diagnosis.

6. Patient 168.648.18699 had a history of benign colon polyps and duodenal ulcer disease and a current gastrointestinal condition of esophagitis (GERD) at study entry. Fecal occult blood results were negative at Baseline. The patient had mild intermittent diarrhea from Day 7 to Day 105 that was considered not related to the study medication by the Investigator and was not of clinical concern. On Day 53, the patient was diagnosed with *C. difficile* colitis of severe intensity that was reported as a SAE and not related to study drug by the Investigator. The event lasted 17 days and study drug was stopped; the patient was discontinued from the study due to the gastrointestinal SAE of clinical concern. As a result of the event, this patient had fecal occult blood tests recorded specifically by the Investigator (CSR 168 Appendix D, Listing 13). Fecal occult blood results were positive at the time of the GIAE on Day 62. Melena was observed on gastrointestinal symptom assessment. A colonoscopy was performed on Day 162 (14 August 2002). The patient had diminutive polyps in the colon removed at 15cm (sigmoid colon) and 30cm for biopsy. The pathology report revealed hyperplasia in both polyps, but no evidence of significant cellular atypia. The remaining mucosa was normal except for internal hemorrhoids [1/24/03 update\120 day safety update.pdf:74-6].

None of these six patients with GIAEs of concern who received SB 207499 were found to have lesions consistent with ischemic colitis, although there was no indication that any specific attention had been directed at the transverse colon to identify lesions consistent with ischemia [clinstat\156.pdf: 73-6, 78-85, 88-9, 1057-89, 1/31/03 clinstat\168.pdf:614-40].

II.B.8.d.ii. PATIENTS WITH GI SYMPTOMS REPORTED AS AES

1. Patient 156.478.15560 (SB 207499 treatment group) experienced AEs of diarrhea on Days 53 and 87 and gastroesophageal reflux on Day 61. All FOB results were negative. A colonoscopy was performed on Day 171 (24 Oct 2001). There was no evidence of significant pathology in the entire examined colon. Several small polyps were removed but microscopic analysis revealed normal tissue.

2. Patient 156.496.14728 (SB 207499 treatment group) experienced an AE of diarrhea on Day 2. The patient had positive FOB results on Days 166 and 167 but a negative result on Day 168. A colonoscopy was performed on Day 135 (28 Aug 2001). Multiple colon polyps were removed during the procedure and diverticulosis of the left colon was observed. All polyps were benign.

3. Patient 168.625.18440 (treated with SB 207499) had no prior gastrointestinal medical history. Fecal occult blood results were negative at Baseline and Days 82-84. The patient experienced a hernia in the right groin area on Day 29, with symptoms lasting 41 days, that was moderate in intensity and considered not related to the study medication by the Investigator. The patient was referred to a gastrointestinal specialist for a colonoscopy during the event. The patient reported a recent change in bowel habit with severe epigastric and left lower quadrant pain. An elective colonoscopy was performed on Day 55 (02 January 2002) and revealed single benign-appearing polyps in the rectum, sigmoid colon, and transverse colon, as well as internal hemorrhoids. The polyps and normal-appearing mucosa from the colon were removed for biopsy. The pathology report noted hyperplasia in each polyp and no histopathologic changes in the sample of colonic mucosa. The diagnostic impression was irritable bowel syndrome. The benign colon polyps were reported as an AE on Day 54 of mild intensity and considered not related to the study medication by the Investigator.

4. Patient 168.648.18372 (treated with SB 207499) had a history of melena, hepatitis, and cholecystectomy and had constipation at study entry. Fecal occult blood results were negative at Baseline and Week 12 (Days 92-94). The patient experienced diarrhea on Day 1 that was mild in intensity and judged unlikely related to study medication by the Investigator; the event resolved in one day. An elective colonoscopy was performed on Day 49 (30 July 2002) due to a heme positive stool. The rectal exam revealed large non- bleeding external hemorrhoids. The doctor was unable to reach the cecum and colon due to a tortuous colon and because the quality of the preparation was poor, precluding a complete examination.

None of these four patients showed evidence of ischemic colitis. Together with the six patients who reported GIAEs of concern, this constitutes 10 patients treated with SB 207499 from the trials 157 and 168 who had colonoscopies because of abdominal complaints who did not show evidence of ischemic colitis [clinstat\156.pdf:1057-89, 1/31/03 clinstat\168.pdf:614-40, 1/24/03 update\120 day safety update.pdf:71].

II.B.9. FECAL OCCULT BLOOD (FOB)

FOBs were not evaluated in the Phase II dose-ranging studies or in the asthma studies. In all Phase III COPD studies, routine FOBs were conducted at Screening and at the end of the treatment period or early withdrawal. In addition, FOBs were supposed to have been conducted for all GIAEs of concern [clinstat\iss\iss.pdf:335, 1/24/03 120 day safety update.pdf:138]. GIAEs of concern are defined under the section of this ISS that reviewed them (see: GASTROINTESTINAL ADVERSE EVENTS OF CONCERN).

NDA #21573 (12/24/02, N-000) ISS: NUMBER AND PERCENTAGE OF COPD PATIENTS WITH ON-THERAPY FECAL OCCULT BLOOD RESULTS, PHASE 3 STUDIES [clinstat\iss\iss.pdf:335, 1/24/03 120 day safety update.pdf:138]√				
			Double-Blind Period	
Treatment Group	Baseline	Number Of Patients Tested	Negative n (%)*	Positive n (%)*
Placebo	negative	955	939 (98.3)	16 (1.7)
	positive	3	3 (100)	0
	missing	12	12 (100)	0
SB 207499	negative	1488	1455 (97.8)	33 (2.2)
	positive	6	5 (83.3)	1 (16.7)
	missing	10	10 (100)	0
* Percentages are calculated based on the row totals for each treatment.				

A table of the 49 patients who were FOB negative at baseline and who became FOB positive sometime during the double-blind period was presented as a set of limited narratives. The following simplified table is extracted from them [clinstat\iss\iss.pdf:336-41, 1/24/05 update\120 day safety update.pdf:140-5]. About half of the patients developing a positive FOB during treatment reported frank melena and these were distributed with about the same frequency in both treatment groups (n.b. 2:1 randomization in most Phase 3 studies). Disturbingly, 15 of the 23 patients reporting melena were NOT included in the category of gastrointestinal adverse events (GIAE) of concern. Even more disturbing is that only 5 of the 49 middle-aged and elderly patients reporting FOB were evaluated by a colonoscopy.

NDA #21573 (12/24/02, N-000) ISS: REPORTING AND EVALUATION OF COPY PATIENTS WITH POSITIVE FECAL OCCULT BLOOD DURING TREATMENT WHO WERE NEGATIVE AT BASELINE, PHASE 3 STUDIES [clinstat\iss\iss.pdf:336-41, 1/24/03 update\120 day safety update.pdf:140-5]√		
Measure	Placebo	SB 207499 15 mg twice daily
Total Patients	16	33
number of FOB-positive stool samples	31	67
patients with at least one GIAE of concern	7	15
patients with melena	8	15
patients with melena NOT reported as a GIAE of concern	6	9
patients receiving colonoscopy	2*	3**
* one patient was evaluated for melena, the other for abdominal pain		
** one patient was evaluated for hemorrhoids, one for melena and abdominal pain and one for melena alone		

II.B.10. PREGNANCIES

No pregnancies were reported during the controlled clinical studies in COPD and asthma patients [clinstat\iss\iss.pdf:248, 1/24/03 update\120 day safety update.pdf:91].

II.B.11. LABORATORY DATA IN CLINICAL STUDIES

In each of the controlled studies, laboratory evaluations, including complete blood counts and serum chemistries, were performed at baseline, prior to exposure to study drug, and at all scheduled study visits, including study conclusion. In some studies,

urinalyses were also performed. Because no clinically important changes were seen in urine variables, urinalysis data are not discussed in this summary. The tables and discussion center around six hematology variables (hemoglobin, hematocrit, WBC, total or absolute neutrophil count, total or absolute eosinophil count, and platelet count) and 11 serum chemistry variables (AST, ALT, GGT, total bilirubin, alkaline phosphatase, creatinine, BUN, sodium, potassium, random glucose, and uric acid), by study group.

Patients who changed from normal values to abnormal values or to abnormal values of concern at any time during the study are summarized for each study group. In these presentations, each study participant with a normal value at baseline may contribute their highest and/or lowest on-therapy value for each variable, using the most extreme value(s) recorded during the study. That is, patients may be counted more than once. It should be noted that serum glucose evaluations were not uniform across studies with respect to food intake (fasting versus random) and in many studies the serum samples were obtained without designation of fasted versus non-fasted status. To assure that clinically significant glucose changes were not missed in this population at risk for adult-onset diabetes (because of age), a value of 8.0mmol/L was set as the value of potential clinical concern for hyperglycemia. While this value is appropriate for fasted patients, it is below the level of clinical concern for recently fed subjects generating the possibility of a lot of "abnormal" glucose values that are really "fed" values and possibly "normal". Sponsor-defined laboratory ranges of concern are presented in the following table [clinstat\iss\iss.pdf:249-50, 258, 260].

NDA #21573 (12/24/02, N-000) ISS: SPONSOR-DEFINED LABORATORY VALUES OF CLINICAL CONCERN [clinstat\iss\iss.pdf:251, 1/24/03 update\120 day safety update.pdf:93, 4/11/03 clinstat\Table27.pdf:1]

Variable	Low Value Of Concern	Low Range	High range	High Value Of Concern
hemoglobin	<0.8xLLN	[0.8xLLN - 1xLLN)	(1xULN - 1.2xULN]	>1.2xULN
hematocrit	<0.8xLLN	[0.8xLLN - 1xLLN)	(1xULN - 1.2xULN]	>1.2xULN
WBC	≤3.0x10^9/L	(3.0x10^9/L - 1xLLN)	(1xULN - 20.0x10^9/L)	≥20.0x10^9/L
total neutrophils	<0.8xLLN	[0.8xLLN - 1xLLN)	(1xULN - 1.5xULN]	>1.5xULN
eosinophils	ND	ND	(1xULN - 2xULN]	>2xULN
platelet count	<100x10^9/L	[100x10^9/L - 1xLLN)	(1xULN - 500x10^9/L]	>500x10^9/L
AST (SGOT)	ND	ND	(1xULN - 2xULN]	>2xULN
ALT (SGPT)	ND	ND	(1xULN - 2xULN]	>2xULN
GGT	ND	ND	(1xULN - 2.5xULN]	>2.5xULN
total bilirubin	ND	ND	(1xULN - 1.5xULN]	>1.5xULN
alk. phos	ND	ND	1xULN - (2.0xULN)	>2.0xULN
creatinine	<0.5xLLN	[0.5xLLN - 1xLLN)	(1xULN - 1.5xULN]	>1.5xULN
BUN (SI units)	ND	ND	(1xULN - 17.85mmol/L]	>17.85mmol/L
(non-SI units)	ND	ND	(1xULN - 50mg/dL]	>50mg/dL
Na^+ (SI units)	≤130mmol/L	(130mmol/L - 1xLLN)	(1xULN - 150mmol/L)	≥150mmol/L
(non-SI units)	≤130mEq/L	(130mEq/L - 1xLLN)	(1xULN - 150mEq/L)	≥150mEq/L
K^+ (SI units)	≤3.0mmol/L	(3.0mmol/L - 1xLLN)	(1xULN - 5.5mmol/L)	≥5.5mmol/L
(non-SI units)	≤3.0mEq/L	(3.0mEq/L - 1xLLN)	(1xULN - 5.5mEq/L)	≥5.5mEq/L
glucose (random)	<	[2.0mmol/L - 1xLLN)	(1xULN - 8.0mmol/L]	>8.0mmol/L
uric acid	ND	ND	(1xULN - 1.4xULN]	>1.4xULN

LLN = Lower Limit of Normal ULN = Upper Limiit of Normal ND = Not Defined

Note: (x - y] = value >x and ≤y; [x - y) = value ≥x and <y; (x - y) = value >x and <y

The numbers (%) of patients with normal values at baseline and on-therapy abnormal values or abnormal values of concern are shown in the tables that follow for hematology and clinical chemistry, sequentially. Patients were assigned to categories based on their highest and/or lowest on-therapy value. Patients with on-therapy values who met criteria for both high and low values of interest and concern were reported in both categories, if applicable [clinstat\iss\iss.pdf:257-8, 1/24/03 update\120 day safety update.pdf:100]. To maximize an ability to find drug-related aberrations, the high dose SB 207499 treatment group (15 mg administered twice daily) will be compared to the placebo group.

These shift tables can be analyzed in a variety of ways. Within a single treatment, the null hypothesis is that shifts from baseline to higher-than-normal and to lower-than-normal values on-treatment should be equal. When a control (e.g., placebo) is available, as is the case here, then shifts up and down from normal in the treatment group should be reflected by similar frequencies of shifts in similar directions in the control group, if there is not true difference between the two treatment groups.

For all hematology variables, shifts for both treatments were qualitatively and quantitatively similar. Regardless of treatment, the percentage of patients shifting from normal to lower-than-normal were slightly greater than those shifting to higher-than-normal for hemoglobin. Exactly the reverse was true for hematocrit, where the percentages shifting from normal to higher-than-normal were a bit more than those shifting to lower-than-normal. WBCs and neutrophils also showed a greater percentage of both treatment groups shifting to higher-than-normal values than to lower-than-normal. Shifts in both directions were about equal for platelets. In the absence of treatment differences, none of this is very meaningful.

NDA #21573 (12/24/02, N-000) ISS: TRANSITIONS FROM NORMAL RANGE AT BASELINE FOR HEMATOLOGY LABORATORY VALUES OF PLACEBO AND SB 207499 (15 mg TWICE DAILY) TREATMENT GROUPS FOR COPD AND ASTHMA PATIENTS IN ALL CONTROLLED STUDIES, THE SAFETY POPULATION [clinstat\iss\iss.pdf:257-8, 1/24/03 update\120 day safety update.pdf:99-100]√

Variable	N[a]	On-Therapy				
		Low Concern n (%)	Low n (%)	Normal n (%)	High n (%)	High Concern n (%)
HEMOGLOBIN (g/L)						
Placebo	1534	3 (0.2)	97 (6.3)	1352 (88.1)	82 (5.3)	1 (0.1)
SB 207499 15 mg BID	2107	4 (0.2)	131 (6.2)	1882 (89.3)	90 (4.3)	2 (0.1)
HEMATOCRIT (%)						
Placebo	1439	3 (0.2)	98 (6.8)	1175 (81.7)	162 (11.3)	3 (0.2)
SB 207499 15 mg BID	2026	3 (0.1)	144 (7.1)	1675 (82.7)	202 (10.0)	4 (0.2)
WBC (10^9/L)						
Placebo	1583	2 (0.1)	26 (1.6)	1395 (88.1)	160 (10.1)	0
SB 207499 15 mg BID	2181	6 (0.3)	36 (1.7)	1916 (87.8)	224 (10.3)	0
NEUTROPHILS ABSOLUTE (10^9/L)						
Placebo	1226	11 (0.9)	17 (1.4)	1079 (88.0)	107 (8.7)	14 (1.1)
SB 207499 15 mg BID	1924	7 (0.4)	28 (1.5)	1711 (88.9)	159 (8.3)	21 (1.1)

NDA #21573 (12/24/02, N-000) ISS: TRANSITIONS FROM NORMAL RANGE AT BASELINE FOR HEMATOLOGY LABORATORY VALUES OF PLACEBO AND SB 207499 (15 mg TWICE DAILY) TREATMENT GROUPS FOR COPD AND ASTHMA PATIENTS IN ALL CONTROLLED STUDIES, THE SAFETY POPULATION [clinstat\iss\iss.pdf:257-8, 1/24/03 update\120 day safety update.pdf:99-100]√

Variable	N[a]	On-Therapy				
		Low Concern n (%)	Low n (%)	Normal n (%)	High n (%)	High Concern n (%)
EOSINOPHILS ABSOLUTE (10^9/L)						
Placebo	1240	NA	NA	1130 (91.1)	104 (8.4)	6 (0.5)
SB 207499 15 mg BID	1940	NA	NA	1816 (93.6)	120 (6.2)	4 (0.2)
PLATELET COUNT (10^9/L)						
Placebo	1639	13 (0.8)	39 (2.4)	1535 (93.7)	50 (3.1)	3 (0.2)
SB 207499 15 mg BID	2214	14 (0.6)	40 (1.8)	2083 (94.1)	67 (3.0)	11 (0.5)

[a] = Number of patients with values within the normal range at baseline. Percentages are based on the number of patients with values within the normal range.

NA = Not Applicable

BID = *bis in deum* = twice daily

Note: Patients with on-therapy values who meet criteria for both high and low values of interest and concern are reported in both categories, if applicable. Patients are assigned to categories based on their highest and/or lowest on-therapy value.

Shifts in eleven laboratory variables that were normal at baseline are presented in the table that follows. For most of these, only patients shifting to higher-than-normal during treatment are shown. Variables that showed a slightly higher percentage of shifts to higher-than-normal for SB 207499-treated patients than for patients who received placebo included Total Bilirubin, Sodium and Glucose. An oddity lay in the serum Potassium which showed more patients shifting to the category of "high concern" than to the category of "high" for both treatments. This probably says more about the choice of a cut-off for "high concern" than it does about any safety problems with SB 207499.

NDA #21573 (12/24/02, N-000) ISS: TRANSITIONS FROM NORMAL RANGE AT BASELINE FOR CHEMISTRY LABORATORY VALUES OF PLACEBO AND SB 207499 (15 mg TWICE DAILY) TREATMENT GROUPS FOR COPD AND ASTHMA PATIENTS IN ALL CONTROLLED STUDIES, THE SAFETY POPULATION [clinstat\iss\iss.pdf:259-60, 1/24/03 update\120 day safety update.pdf:101-2]√

Variable	N[a]	On-Therapy				
		Low Concern n (%)	Low n (%)	Normal n (%)	High n (%)	High Concern n (%)
AST (IU/L)						
Placebo	1673	NA	NA	1626 (97.2)	39 (2.3)	8 (0.5)
SB 207499 15 mg BID	2272	NA	NA	2216 (97.5)	50 (2.2)	6 (0.3)
ALT (IU/L)						
Placebo	1647	NA	NA	1574 (95.6)	69 (4.2)	4 (0.2)
SB 207499 15 mg BID	2259	NA	NA	2181 (96.5)	73 (3.2)	5 (0.2)
GGT (IU/L)						
Placebo	1540	NA	NA	1443 (93.7)	90 (5.8)	7 (0.5)
SB 207499 15 mg BID	2070	NA	NA	1970 (95.2)	97 (4.7)	3 (0.1)
TOTAL BILIRUBIN (micromol/L)						
Placebo	1682	NA	NA	1622 (96.4)	47 (2.8)	13 (0.8)
SB 207499 15 mg BID	2264	NA	NA	2171 (95.9)	87 (3.8)	6 (0.3)
ALKALINE PHOSPHATASE (IU/L)						
Placebo	1641	NA	NA	1599 (97.4)	41 (2.5)	1 (0.1)

NDA #21573 (12/24/02, N-000) ISS: TRANSITIONS FROM NORMAL RANGE AT BASELINE FOR CHEMISTRY LABORATORY VALUES OF PLACEBO AND SB 207499 (15 mg TWICE DAILY) TREATMENT GROUPS FOR COPD AND ASTHMA PATIENTS IN ALL CONTROLLED STUDIES, THE SAFETY POPULATION [clinstat\iss\iss.pdf:259-60, 1/24/03 update\120 day safety update.pdf:101-2]√

Variable	N[a]	On-Therapy				
		Low Concern n (%)	Low n (%)	Normal n (%)	High n (%)	High Concern n (%)
SB 207499 15 mg BID	2230	NA	NA	2171 (97.4)	58 (2.6)	1 (0.0)
CREATININE (micromol/L)						
Placebo	1641	0	32 (2.0)	1554 (94.7)	51 (3.1)	5 (0.3)
SB 207499 15 mg BID	2239	0	57 (2.5)	2121 (94.7)	53 (2.4)	8 (0.4)
BUN (mmol/L)						
Placebo	1669	NA	NA	1582 (94.8)	85 (5.1)	2 (0.1)
SB 207499 15 mg BID	2254	NA	NA	2157 (95.7)	94 (4.2)	3 (0.1)
SODIUM (mmol/L)						
Placebo	1650	6 (0.4)	73 (4.4)	1481 (89.8)	74 (4.5)	17 (1.0)
SB 207499 15 mg BID	2232	9 (0.4)	95 (4.3)	1996 (89.4)	105 (4.7)	28 (1.3)
POTASSIUM (mmol/L)						
Placebo	1631	0	15 (0.9)	1470 (90.1)	40 (2.5)	106 (6.5)
SB 207499 15 mg BID	2208	1 (0.0)	26 (1.2)	1978 (89.6)	73 (3.3)	130 (5.9)
GLUCOSE, RANDOM (mmol/L)						
Placebo	1284	4 (0.3)	117 (9.1)	848 (66.0)	194 (15.1)	130 (10.1)
SB 207499 15 mg BID	1705	2 (0.1)	137 (8.0)	1138 (66.7)	259 (15.2)	190 (11.1)
URIC ACID (micromol/L)						
Placebo	1653	NA	NA	1583 (95.8)	69 (4.2)	1 (0.1)
SB 207499 15 mg BID	2243	NA	NA	2166 (96.6)	76 (3.4)	1 (0.0)

[a] = Number of patients with values within the normal range at baseline. Percentages are based on the number of patients with values within the normal range.

NA = Not Applicable

BID = *bis in deum* = twice daily

Note: Patients with on-therapy values who meet criteria for both high and low values of interest and concern are reported in both categories, if applicable. Patients are assigned to categories based on their highest and/or lowest on-therapy value.

II.B.12. VITAL SIGNS

In all controlled studies in COPD and asthma patients, blood pressure and heart rate were measured at all visits after the patient had been sitting for 5 minutes and after a defined time since beta-adrenergic agonists had been taken. In Studies 039, 042, 076, 091 and 110 vital signs were obtained at least 2 hours after albuterol administration; in Studies 111, 156 and 168 at least 4 hours after albuterol.

In Studies 039, 042, 076, 091, 110, 111, 156 and 168 orthostatic changes in vital signs were measured at predefined visits, including Screening, Baseline, Endpoint, at Early Withdrawal and at visits associated with GIAEs of concern. Orthostatic changes in heart rate and blood pressure were obtained by measurement after the patient had been supine for 5 minutes and then after sitting with legs dependent for 1 minute.

Vital signs of concern were identified and tabulated. Sponsor-defined vital sign values or orthostatic vital sign changes of concern are defined in the following table.

Any orthostatic vital sign associated with a GIAE of concern or any vital signs reported as adverse events are presented in the relevant section of this review [clinstat\iss\iss.pdf:285, 1/24/03 update\120 day safety update.pdf:109].

NDA #21573 (12/24/02, N-000) ISS: SPONSOR-DEFINED VITAL SIGNS VALUES OF CLINICAL CONCERN [clinstat\iss\iss.pdf:286, 1/24/03 update\120 day safety update.pdf:110]√

Variable	Low Value Of Concern	Low Range	High range	High Value Of Concern
systolic BP (mm Hg)	<75	75-89	140-180	>180
diastolic BP (mm Hg)	<50	50-59	90-110	>110
heart rate (bpm)	<50	50-59	100-120	>120
orthostatic change[a] in systolic BP (mm Hg)	ND	ND	DEC 10-19	DEC ≥ 20
orthostatic change[a] in diastolic BP (mm Hg)	ND	ND	ND	DEC ≥ 10
orthostatic chantge[a] in HR (bpm)	ND	ND	ND	INC ≥ 10

[a] = Orthostatic change assessed as change between supine for 5 minutes followed by sitting with legs dependent for 1 minute.
ND = Not Defined DEC = Decrease INC = Increase

Shifts to higher-than-normal systolic BP, diastolic BP and heart rate were much more common than shifts to lower-than-normal values. However, these percentage changes were quantitatively similar in the high-dose SB 207499 (15 mg twice daily) group and the placebo group, as can be seen in the following table.

N DA #21573 (12/24/02, N-000) ISS: TRANSITIONS FROM NORMAL RANGE AT BASELINE FOR VITAL SIGNS OF PLACEBO AND SB 207499 (15 mg TWICE DAILY) TREATMENT GROUPS FOR COPD AND ASTHMA PATIENTS IN ALL CONTROLLED STUDIES, THE SAFETY POPULATION [clinstat\iss\iss.pdf:288, 1/24/03 update\120 day safety update.pdf:112]√

Variable	N[b]	On-Therapy[a]				
		Low Concern n (%)	Low n (%)	Normal n (%)	High n (%)	High Concern n (%)
SITTING SYSTOLIC BLOOD PRESSURE (mm Hg)						
Placebo	1175	0	5 (0.4)	723 (61.5)	444 (37.8)	3 (0.3)
SB 207499 15 mg BID	1568	1 (0.1)	15 (1.0)	945 (60.3)	603 (38.5)	4 (0.3)
SITTING DIASTOLIC BLOOD PRESSURE (mm Hg)						
Placebo	1500	3 (0.2)	78 (5.2)	1078 (71.9)	340 (22.7)	6 (0.4)
SB 207499 15 mg BID	1990	5 (0.3)	105 (5.3)	1431 (71.9)	449 (22.6)	3 (0.2)
HEART RATE (bpm)						
Placebo	1644	8 (0.5)	132 (8.0)	1388 (84.4)	115 (7.0)	3 (0.2)
SB 207499 15 mg BID	2236	15 (0.7)	208 (9.3)	1828 (81.8)	180 (8.1)	8 (0.4)

[a] = Patients are assigned to categories based on their highest and/or lowest on-therapy value..

[b] = Number of patients with values within the normal range at baseline. Percentages are based on the number of patients with values within the normal range at a baseline.

BID = *bis in deum* = twice daily

Note: Patients with on-therapy values who meet criteria for both high and low values of interest and concern are reported in both categories, if applicable. Patients are assigned to categories based on their highest and/or lowest on-therapy value.

II.B.13. CARDIOVASCULAR SAFETY

II.B.13.a. TROUGH ELECTROCARDIOGRAMS

More than 70,000 ECGs were obtained for analysis across the SB 207499 asthma and COPD program including the long-term safety program. A 12-lead ECG was performed during run-in visits and double-blind treatment periods, upon early withdrawal and at Safety Follow-up (if there were ECG abnormalities at the previous visit). In the Phase III pivotal studies, an ECG was also obtained at Baseline, Day 1 and Week 24 (Endpoint). An ECG was also recorded 3 hours after administration of study medication (estimated C_{Max}).

In mechanism of action studies, dose-ranging studies and asthma studies, ECGs were locally interpreted. For the Phase III pivotal studies, standardized 12-lead ECG equipment and a procedures manual were provided to all sites. The ECGs from Phase III studies were transmitted electronically via modem to a centralized facility (Biomedical Systems, Brussels, Belgium or St Louis, Missouri, USA) for interpretation by a Board Certified cardiologist and data processing. Clinically significant changes were recorded by the Investigator as adverse events. ECG values of concern were identified and tabulated.

The Marquette 12-lead ECG machine determined the median QT interval for each lead. It then calculated the QT interval across all leads (a more detailed description is provided in the manufacturer's literature). QT values were corrected by applying the Bazett correction factor using the following formula:

NDA #21573 (12/24/02, N-000) ISS: BAZETT'S QT INTERVAL CORRECTION [clinstat\iss\iss.pdf:299, 1/24/03 update\120 day safety update.pdf:117]√
QTc = UQT / SQRT (60/VR)
(corrected QT = [uncorrected QT] divided by [square root of (60 divided by Ventricular Rate)]

Any QTc values greater than 500msec were manually verified by the supervisory cardiologist who over-read ECGs meeting this criterion. Sponsor-defined categories of change from baseline to highest and lowest on-treatment values were established for the many ECG variables [clinstat\iss\iss.pdf:300, 1/24/03 update\120 day safety updat.pdf:116-8]:

NDA #21573 (12/24/02, N-000) ISS: SPONSOR-DEFINED ELECTROCARDIOGRAPHIC VARIABLE VALUES OF CLINICAL CONCERN [clinstat\iss\iss.pdf:300, 1/24/03 update\120 day safety update.pdf:118]√				
Variable	**Low Value Of Concern**	**Low Range**	**High range**	**High Value Of Concern**
QRS interval (msec)	NA	NA	120-199	≥200
PR interval (msec)	NA	NA	200-249	>250
atrial rate (bpm)	<50 and 2 bpm lower than nadir from baseline or < 45 bpm	45-55	100-120	>120
ventricular rate (bpm)	<50 and 2 bpm lower than nadir from baseline or < 45 bpm	45-55	100-120	>120

NDA #21573 (12/24/02, N-000) ISS: SPONSOR-DEFINED ELECTROCARDIOGRAPHIC VARIABLE VALUES OF CLINICAL CONCERN [clinstat\iss\iss.pdf:300, 1/24/03 update\120 day safety update.pdf:118]√				
Variable	**Low Value Of Concern**	**Low Range**	**High range**	**High Value Of Concern**
QTc interval (msec)[a]	NA	NA	male 430-450 (borderline) female 450-470 (borderline)	male >450 (prolonged) female >470 (prolonged)
QTc change from baseline (msec)[a]	NA	NA	increased 30-60	increase >60
QT uncorrected (msec)	NA	NA	NA	≥500
QRS axis[b] (degrees)				change from normal baseline (-30 to +90) of ± 30 degrees with normal baseline QRS duration (<120 msec)
[a] = QT corrected by Bazett's formula [b] = QRS evaluations are only presented for Phase 3 studies.				

The numbers (%) of patients from all controlled studies with transitions from Baseline ECG variables to on-therapy values outside the normal range (low or high) for placebo- and SB 207499-treated patients are presented in the following table [clinstat\iss\iss.pdf:299-300, 304-5, 1/24/03 update\120 day safety update.pdf:121-2]. By inspection, the only differences between treatments were more shifts to rapid atrial and ventricular rates and more shifts to longer QRS durations, PR and QTc intervals in the SB 207499 group than in placebo. The QTc is particularly interesting because Bazett's correction is known to over-correct for heart rate elevations. SB 207499 treatment is associated with shifts to faster rates than placebo and the corresponding shifts to higher-than-normal QTc should be lower for SB 207499 than placebo if heart rate was the only difference between treatment groups. The slightly greater percentage of SB 207499 patients showing shifts to higher-than-normal QTc than placebo patients at least raised the possibility there was an independent effect of SB 207499 on QTc prolongation. The QTc change from baseline did not show this treatment difference, thus it did not corroborate this speculation.

NDA #21573 (12/24/02, N-000) ISS: TRANSITIONS FROM NORMAL RANGE AT BASELINE FOR TROUGH ECG VALUES OF PLACEBO AND SB 207499 (15 mg TWICE DAILY) TREATMENT GROUPS FOR COPD AND ASTHMA PATIENTS IN ALL CONTROLLED STUDIES, THE SAFETY POPULATION [clinstat\iss\iss.pdf:304-5, 1/24/03 update\120 day safety update.pdf:121-2, 1/24/03 update\120 day safety update.pdf:121-2]√						
Variable	**N[b]**	**On-Therapy[a]**				
		Low Concern n (%)	**Low n (%)**	**Normal n (%)**	**High n (%)**	**High Concern n (%)**
ATRIAL RATE (bpm)						
Placebo	1553	15 (1.0)	134 (8.6)	1302 (83.8)	95 (6.1)	12 (0.8)
SB 207499 15 mg BID	2083	24 (1.2)	160 (7.7)	1724 (82.8)	165 (7.9)	14 (0.7)
VENTRICULAR RATE (bpm)						
Placebo	1563	16 (1.0)	134 (8.6)	1315 (84.1)	96 (6.1)	7 (0.4)
SB 207499 15 mg BID	2098	24 (1.1)	164 (7.8)	1734 (82.7)	168 (8.0)	13 (0.6)
QRS DURATION (msec)						
Placebo	1613	NA	NA	1565 (97.0)	46 (2.9)	2 (0.1)

NDA #21573 (12/24/02, N-000) ISS: TRANSITIONS FROM NORMAL RANGE AT BASELINE FOR TROUGH ECG VALUES OF PLACEBO AND SB 207499 (15 mg TWICE DAILY) TREATMENT GROUPS FOR COPD AND ASTHMA PATIENTS IN ALL CONTROLLED STUDIES, THE SAFETY POPULATION [clinstat\iss\iss.pdf:304-5, 1/24/03 update\120 day safety update.pdf:121-2, 1/24/03 update\120 day safety update.pdf:121-2]√

Variable	N[b]	On-Therapy[a]				
		Low Concern n (%)	Low n (%)	Normal n (%)	High n (%)	High Concern n (%)
SB 207499 15 mg BID	2163	NA	NA	2080 (96.2)	82 (3.8)	1 (0.0)
PR INTERVAL (msec)						
Placebo	1589	NA	NA	1503 (94.6)	82 (5.2)	4 (0.3)
SB 207499 15 mg BID	2104	NA	NA	1962 (93.3)	140 (6.7)	2 (0.1)
QTc INTERVAL (msec)[c]						
Placebo	1316	NA	NA	921 (70.0)	274 (20.8)	121 (9.2)
SB 207499 15 mg BID	1723	NA	NA	1181 (68.5)	407 (23.6)	135 (7.8)
QT INTERVAL (msec)						
Placebo	1691	NA	NA	1679 (99.3)	NA	12 (0.7)
SB 207499 15 mg BID	2274	NA	NA	2265 (99.6)	NA	9 (0.4)
QTc CHANGE FROM BASELINE (msec)[d]						
Placebo	1316	NA	NA	1038 (78.9)	233 (17.7)	45 (3.4)
SB 207499 15 mg BID	1723	NA	NA	1390 (80.7)	282 (16.4)	51 (3.0)

[a] = Patients are assigned to categories based on their highest and/or lowest on-therapy value. Patients with on-therapy values who meet criteria for both high and low values of interest and concern are reported in both categories, if applicable.

[b] = Number of patients with values within the normal range at baseline. Percentages are based on the number of patients with values within the normal range at baseline.

[c] = QT corrected by Bazett's formula.

[d] = Number of patients with values within the normal range at baseline. Percentages are based on the number of patients with values within the normal range at baseline.

NA = Not Applicable

BID = *bis in deum* = twice daily

Axis shifts from normal are shown in the table below [1/24/03 update\120 day safety update.pdf:122]. Both left and right axis shifts seemed to show dose-ordering among the various doses of SB 207499. However, the frequency of shifts, both left and right, in the high-dose SB 207499 group was not much different from the placebo group.

NDA #21573 (12/24/02, N-000) ISS: TRANSITIONS FROM NORMAL RANGE AT BASELINE FOR ECG QRS AXIS VALUES OF PLACEBO AND SB 207499 TREATMENT GROUPS FOR COPD PATIENTS IN ALL PHASE 3 CONTROLLED STUDIES [clinstat\iss\iss.pdf:307-8, 318, 1/24/03 update\120 day safety update.pdf:122, 1717-8]√

QRS Axis	N[b]	On-Therapy[a]			
		LAD[c] n (%)	Normal n (%)	RAD[d] n (%)	Indeterminate n (%)
Placebo	1509	49 (3.2)	1404 (93.0)	55 (3.6)	3 (0.2)
SB 207499 2.5 mg BID	61	0	61 (100.0)	0	0
SB 207499 5 mg BID	296	4 (1.4)	286 (96.6)	6 (2.0)	0
SB 207499 10 mg BID	338	5 (1.5)	325 (96.2)	7 (2.1)	1 (0.3)
SB 207499 15 mg BID	1961	81 (4.1)	1778 (90.7)	94 (4.8)	14 (0.7)

NDA #21573 (12/24/02, N-000) ISS: TRANSITIONS FROM NORMAL RANGE AT BASELINE FOR ECG QRS AXIS VALUES OF PLACEBO AND SB 207499 TREATMENT GROUPS FOR COPD PATIENTS IN ALL PHASE 3 CONTROLLED STUDIES [clinstat\iss\iss.pdf:307-8, 318, 1/24/03 update\120 day safety update.pdf:122, 1717-8]√

QRS Axis	N[b]	On-Therapy[a] LAD[c] n (%)	Normal n (%)	RAD[d] n (%)	Indeterminate n (%)

[a] = Patients are assigned to categories based on their highest and/or lowest on-therapy value. Patients with on-therapy values who meet criteria for both high and low values of interest and concern are reported in both categories, if applicable.

[b] = Number of patients with values within the normal range at baseline. Percentages are based on the number of patients with values within the normal range at baseline.

[c] = Left Axis Deviation

[d] = Right Axis Deviation

BID = *bis in deum* = twice daily

The most frequent (defined as occurring in >1% of patients in any treatment group) on-therapy ECG abnormalities that were not present on ECGs recorded pre-therapy at Screening or Baseline and were more frequent in the high-dose SB 207499 group than the placebo group are presented in the table that follows [clinstat\iss\iss.pdf:306-8, 1/24/03 update\120 day safety update.pdf:124-5].

Not much can be definitively concluded from the table, but there are some interesting observations. First, three categories of old Myocardial Infarction showed up as on-therapy new onset events that were not present at baseline, as did three categories of Ischemia. All were more frequent in the SB 207499 group than in placebo. Left Axis Deviation is a solitary finding, but Left Anterior Hemiblock is frequently defined solely by Left Axis Deviation. Moreover, Left Axis Deviation is one criterion of Left Ventricular Hypertrophy. Taken together, the three of these, which may all represent the same ECG finding, have a frequency in the high-dose SB 207499 group that is little different from the frequency of the same three findings in the placebo-treated patients. Not one of these new-onset ECG abnormalities shows even a trend toward dose-ordering.

NDA #21573 (12/24/02, N-000) ISS: NUMBER (%) OF PATIENTS WITH THE MOST FREQUENTLY (> 1% PATIENTS IN ANY TREATMENT GROUP) REPORTED NEW-ONSET ECG ABNORMALITIES AT TROUGH THAT WERE NOT PRESENT PRE-THERAPY WHERE THE FREQUENCY OF THAT ECG ABNORMALITY IN THE SB 207499 15 mg TWICE DAILY COLUMN WAS GREATER THAN PLACEBO FOR COPD AND ASTHMA PATIENTS IN ALL CONTROLLED STUDIES, THE SAFETY POPULATION [clinstat\iss\iss.pdf:307-8, 1/24/03 update\120 day safety update.pdf:124-5]√

ECG Abnormality	Treatments: Placebo 0 mg bid (N = 1777)[a] n (%)[b]	SB 207499: 2.5 mg bid (N = 70)[a] n (%)[b]	5 mg bid (N = 346)[a] n (%)[b]	10 mg bid (N = 405)[a] n (%)[b]	15 mg bid (N = 2446)[a] n (%)[b]	Total SB (N = 3267)[a] n (%)[b]
sinus bradycardia	144 (9.6)	0	19 (6.0)	13 (3.5)	239 (11.8)	271 (9.8)
QT-interval increased	128 (7.9)	5 (8.5)	9 (2.7)	5 (1.3)	200 (9.1)	219 (7.4)
PACs NOS[c]	115 (6.8)	2 (3.0)	10 (2.9)	5 (1.3)	166 (7.1)	183 (5.8)
poor R-wave progression	96 (6.1)	4 (6.2)	6 (1.8)	5 (1.3)	135 (6.3)	150 (5.1)
intraventricular block NOS[c]	70 (4.1)	3 (4.5)	5 (1.5)	1 (0.3)	139 (5.9)	148 (4.7)
sinus tachycardia	70 (4.1)	3 (4.3)	6 (1.8)	6 (1.5)	128 (5.4)	143 (4.5)
PVCs NOS[c]	43 (2.5)	2 (3.0)	7 (2.1)	4 (1.0)	113 (4.8)	126 (4.0)

NDA #21573 (12/24/02, N-000) ISS: NUMBER (%) OF PATIENTS WITH THE MOST FREQUENTLY (> 1% PATIENTS IN ANY TREATMENT GROUP) REPORTED NEW-ONSET ECG ABNORMALITIES AT TROUGH THAT WERE NOT PRESENT PRE-THERAPY WHERE THE FREQUENCY OF THAT ECG ABNORMALITY IN THE SB 207499 15 mg TWICE DAILY COLUMN WAS GREATER THAN PLACEBO FOR COPD AND ASTHMA PATIENTS IN ALL CONTROLLED STUDIES, THE SAFETY POPULATION [clinstat\iss\iss.pdf:307-8, 1/24/03 update\120 day safety update.pdf:124-5]√

ECG Abnormality	Treatments					
	Placebo	SB 207499				
	0 mg bid (N = 1777)[a] n (%)[b]	2.5 mg bid (N = 70)[a] n (%)[b]	5 mg bid (N = 346)[a] n (%)[b]	10 mg bid (N = 405)[a] n (%)[b]	15 mg bid (N = 2446)[a] n (%)[b]	Total SB (N = 3267)[a] n (%)[b]
atrial hypertrophy	50 (2.9)	0	0	0	87 (3.6)	87 (2.7)
left axis deviation on ECG	56 (3.4)	1 (1.5)	1 (0.3)	4 (1.1)	81 (3.5)	87 (2.8)
MI[d], septal old	46 (2.7)	1 (1.5)	3 (0.9)	0	78 (3.4)	82 (2.7)
1st degree AV block	44 (2.6)	1 (1.5)	5 (1.5)	1 (0.3)	67 (2.9)	74 (2.4)
left anterior hemiblock	41 (2.5)	0	4 (1.2)	3 (0.8)	66 (2.9)	73 (2.4)
right axis deviation on ECG	40 (2.3)	0	3 (0.9)	2 (0.5)	61 (2.6)	66 (2.1)
ectopic atrial beats NOS[c]	29 (1.6)	0	0	0	60 (2.5)	60 (1.8)
right atrial hypertrophy (P-pulmonale)	27 ()1.6	2 (2.9)	0	1 (0.2)	51 (2.1)	54 (1.7)
MI[d], inferior old	21 (1.2)	0	4 (1.2)	3 (0.8)	47 (2.0)	54 (1.7)
bradycardia	19 (1.1)	0	0	0	46 (1.9)	46 (1.4)
left ventricular hypertrophy	23 (1.3)	2 (2.9)	5 (1.5)	5 (1.3)	38 (1.6)	50 (1.6)
ventricular hypertrophy NOS[c]	16 (0.9)	0	0	0	31 (1.3)	31 (1.0)
atrial fibrillation	12 (0.7)	1 (1.4)	0	0	23 (1.0)	24 (0.7)
right bundle branch block	16 (0.9)	0	4 (1.2)	4 (1.0)	23 (1.0)	31 (1.0)
pre-excitation syndrome NOS[c]	5 (0.3)	1 (1.4)	0	0	16 (0.7)	17 (0.5)
myocardial ischemia, inferior	5 (0.3)	1 (1.4)	0	0	12 (0.5)	13 (0.4)
myocardial ischemia, lateral	7 (0.4)	1 (1.4)	0	0	12 (0.5)	13 (0.4)
MI[d], posterior old	1 (0.1)	1 (1.4)	0	0	4 (0.2)	5 (0.2)
ECG findings of ischemia	0	1 (1.4)	0	0	2 (0.1)	3 (0.1)
LAD[e] or LAH[f] or LVH[g]	120 (0.7)	3 (0.4)	10 (0.3)	12 (0.3)	185 (0.8)	210 (0.6)

bid = *bis in deum* = twice daily

[a] = Number of patients without the abnormality pre-therapy.

[b] = Percentages are based on the number of patients without the specific abnormality pre-therapy.

[c] = Not Otherwise Specified

[d] = Myocardial Infarction

[e] = Left Axis Deviation

[f] = Left Anterior Hemiblock

[g] = Left Ventricular Hypertrophy

II.B.13.b. C_{MAX} ELECTROCARDIOGRAMS

An analysis of ECG variables obtained at 3 hours post-dose on Day 1 and Week 24 is presented for the Phase III pivotal studies because ECGs were not obtained at C_{Max} in the mechanism of action studies [clinstat\iss\iss.pdf:324, 328-32]. The higher atrial and ventricular rates for the high-dose SB 207499 group seen in the trough ECG data was not corroborated by the C_{Max} ECG data. As a matter of fact the trough CMax ECGs were largely unrevealing of any discrepancy between the high-dose (15 mg twice daily) SB

207499 group and the placebo group [clinstat\iss\iss.pdf:331-5, 1/24/03 update\120 day safety update.pdf:132].

NDA #21573 (12/24/02, N-000) ISS: TRANSITIONS FROM NORMAL RANGE AT BASELINE FOR CMAX ECG VALUES OF PLACEBO AND SB 207499 (15 mg TWICE DAILY) TREATMENT GROUPS FOR COPD PATIENTS IN THE PIVOTAL PHASE 3 CONTROLLED STUDIES [clinstat\iss\iss.pdf:331-5, 1/24/03 update\120 day safety update.pdf:132]√

Variable	N[b]	On-Therapy[a]				
		Low Concern n (%)	Low n (%)	Normal n (%)	High n (%)	High Concern n (%)
ATRIAL RATE (bpm)						
Placebo	1036	7 (0.7)	63 (6.1)	920 (88.8)	41 (4.0)	5 (0.5)
SB 207499 15 mg BID	1735	9 (0.5)	70 (4.0)	1577 (90.9)	73 (4.2)	7 (0.4)
VENTRICULAR RATE (bpm)						
Placebo	1047	7 (0.7)	63 (6.0)	936 (89.4)	39 (3.7)	2 (0.2)
SB 207499 15 mg BID	1750	9 (0.5)	72 (4.1)	1594 (91.1)	71 (4.1)	4 (0.2)
QRS DURATION (msec)						
Placebo	1072	NA	NA	1053 (98.2)	19 (1.8)	NA
SB 207499 15 mg BID	1815	NA	NA	1789 (98.6)	26 (1.4)	NA
PR INTERVAL (msec)						
Placebo	1056	NA	NA	1037 (98.2)	19 (1.8)	0
SB 207499 15 mg BID	1764	NA	NA	1716 (97.3)	48 (2.7)	0
QTc INTERVAL (msec)[c]						
Placebo	846	NA	NA	682 (80.6)	131 (15.5)	33 (3.9)
SB 207499 15 mg BID	1418	NA	NA	1118 (78.8)	254 (17.9)	46 (3.2)
QT INTERVAL (msec)						
Placebo	1157	NA	NA	1153 (99.7)	NA	4 (0.3)
SB 207499 15 mg BID	1940	NA	NA	1931 (99.5)	NA	9 (0.5)
QTc CHANGE FROM BASELINE (msec)[d]						
Placebo	846	NA	NA	770 ()91.0	68 (8.0)	8 (0.9)
SB 207499 15 mg BID	1418	NA	NA	1305 (92.0)	103 (7.3)	10 (0.7)

[a] = Patients are assigned to categories based on their highest and/or lowest on-therapy value. Patients with on-therapy values who meet criteria for both high and low values of interest and concern are reported in both categories, if applicable.

[b] = Number of patients with values within the normal range at baseline. Percentages are based on the number of patients with values within the normal range at baseline.

[c] = QT corrected by Bazett's formula.

[d] = Number of patients with values within the normal range at baseline. Percentages are based on the number of patients with values within the normal range at baseline.

NA = Not Applicable

BID = *bis in deum* = twice daily

The most frequent (defined as occurring in >1% of patients in any treatment group) on-therapy ECG abnormalities at C_{Max} that were not present on ECGs recorded pre-therapy, at Screening or Baseline, in the Phase III studies is presented below [clinstat\iss\iss.pdf:333].

NDA #21573 (12/24/02, N-000) ISS: NUMBER (%) OF PATIENTS WITH THE MOST FREQUENTLY (> 1% PATIENTS IN ANY TREATMENT GROUP) REPORTED NEW-ONSET ECG ABNORMALITIES AT CMAX THAT WERE NOT PRESENT PRE-THERAPY, WHERE THE FREQUENCY OF THAT ECG ABNORMALITY IN THE SB 207499 15 mg TWICE DAILY COLUMN WAS GREATER THAN PLACEBO FOR COPD PATIENTS IN ALL PIVOTAL PHASE 3 STUDIES [clinstat\iss\iss.pdf:333, 1/24/03 update\120 day safety update.pdf:133]√

ECG Abnormality	Treatment	
	Placebo (N = 1319)[a] n (%)[b]	SB 207499 15 mg BID (N = 2109)[a] n (%)[b]
QT interval increased	49 (4.1)	104 (5.6)
ST changes nonspecific	59 (5.1)	98 (5.2)
premature atrial contractions NOS[c]	30 (2.4)	67 (3.3)
intraventricular contractions NOS[c]	30 (2.4)	57 (2.8)
PVCs unifocal	31 (2.4)	58 (2.8)
sinus tachycardia	29 (2.3)	52 (2.5)
atrial hypertrophy NOS[c]	24 (1.9)	41 (2.0)
premature ventricular contractions NOS[c]	8 (0.6)	39 (1.9)
right axis deviation on ECG	17 (1.3)	36 (1.8)
1st degree AV[d] block	11 (0.9)	26 (1.3)
MI[e], inferior old	10 (0.8)	24 (1.2)
T-wave flat	10 (0.8)	22 (1.1)

[a] = Number of patients without the specific abnormality pre-therapy.
[b] = Percentages are based on the number of patients without the specific abnormality pre-therapy.
[c] = Not Otherwise Specified
[d] = AtrioVentricular
[e] = Myocardial Infarction

II.B.13.c. T-WAVE AXIS ANALYSIS

There have been several recent publications demonstrating the utility of the T-wave axis as an indicator of risk of cardiac events in elderly people in population-based studies. The utility of this measurement in trials of short duration is unknown. In this section, analyses of all T-wave axis data are presented for the Phase 3 pivotal studies (039, 042, 091, 156), the cardiovascular safety study (168) and the long-term safety extension studies (040, 041). Changes of concern in T-wave axis was defined as a change from baseline in T-wave axis of ≥ 30 degrees and a T-wave axis outside of the normal range (< -15 degrees or > +105 degrees) at baseline. This exploratory analysis was not revealing of a safety signal in the SB 207499 high-dose (15 mg twice daily) group [1/24/03 update\120 day safety update.pdf:134-5].

NDA #21573 (12/24/02, N-000) ISS: TRANSITIONS FROM NORMAL RANGE AT BASELINE FOR T-WAVE AXIS VALUES OF PLACEBO AND SB 207499 (15 mg TWICE DAILY) TREATMENT GROUPS FOR COPD PATIENTS IN PHASE 3 CONTROLLED STUDIES, CARDIOVASCULAR SAFETY STUDY AND LONG TERM SAFETY EXTENSION STUDIES [1/24/03 update\120 day safety update.pdf:135]√

Variable	N[b]	On-Therapy[a]	
		Normal n (%)	Concern n (%)
TROUGH			
Placebo	1056	948 (89.8)	108 (10.2)
SB 207499 15 mg BID[c]	1724	1530 (88.7)	194 (11.3)

NDA #21573 (12/24/02, N-000) ISS: TRANSITIONS FROM NORMAL RANGE AT BASELINE FOR T-WAVE AXIS VALUES OF PLACEBO AND SB 207499 (15 mg TWICE DAILY) TREATMENT GROUPS FOR COPD PATIENTS IN PHASE 3 CONTROLLED STUDIES, CARDIOVASCULAR SAFETY STUDY AND LONG TERM SAFETY EXTENSION STUDIES [1/24/03 update\120 day safety update.pdf:135]√

Variable	N[b]	On-Therapy[a]	
		Normal n (%)	Concern n (%)
CMAX			
Placebo	1075	1024 (95.3)	51 (4.7)
SB 207499 15 mg BID[c]	1815	1734 (95.5)	81 (4.5)

[a] = Patients are assigned to categories based on their highest and/or lowest on-therapy value and evaluated in patients with a normal T-wave axis (-15 to +105 degrees) and QRS interval (< 120 ms) at baseline.

[b] = Number and percentages are based on the number of patients within the normal range at baseline.

[c] = *bis in deum* = twice daily

II.B.13.d. HOLTER MONITORING

Integrated Holter monitoring data is found in Study 168, Appendix J. For three of the four Phase III Pivotal Studies, narratives were prepared using criteria outlined within the protocols and were included in the study reports (Table 15.0 in Studies 039, 042 and 091). For these three studies, additional Holter narratives were provided in this Summary, using a set of criteria for Holter values of concern applied uniformly across these three studies. A narrative location table (Appendix 3 of the ISS) identified all patients with additional narratives of patients with Holter findings. Additional Holter narratives of clinical concern were included in Appendix 7 of the ISS. The uniform Holter criteria were incorporated in Study 168 and therefore, narratives for all patients with Holter values of concern were included in the study report (Study 168, Table 15.0). The 120-day safety update added no new information to that submitted in the ISS [clinstat\iss\iss.pdf:334, 1/24/03 update\120 day safety update.pdf:137].

NDA #21573 (12/24/02, N-000) ISS: SUMMARY OF HOLTER PATIENTS AND TREATMENT IN EACH STUDY [clinstat\168.pdf:1530]√

Study	Treatment			
	Placebo		SB 207499	
	Safety Population[a]	FDA Population[b]	Safety Population[a]	FDA Population[b]
039	23	16	50	40
042	22	20	44	31
091	12	5	27	13
168	89	81	170	129
Totals	146	122	291	213

[a] = Patients with at least one Holter monitoring session (may include patients with or without Baseline).

[b] = Includes Baseline or Screening Holter monitoring and two on-therapy Holter monitoring sessions (Week 1 and Week 12 or Week 20).

All Holter sessions listed are ≥ 18 hours.

Demographic characteristics of the subset of patients from the four trials that contributed Holter data were similar for the two treatment groups. There was approximately a 2:1 (SB 207499 to placebo) assignment to the two treatments because that was the randomization ratio of the underlying studies. Overall, males comprised

70% of the data with an about equal frequency in the two treatments (males: placebo = 69.3%, SB 207499 = 71.8%. Both treatment groups were almost exclusively Caucasian (placebo = 95.2%, SB 207499 = 95.5%). Weight and Body Mass Index were about evenly distributed between the two groups. Mean ages and ranges were about equal between the two treatments but older ages, dichotomized at 65 years, were a bit uneven (age ≥ 65 years: placebo = 60.3%, SB 207499 = 53.3%) [clinstat\168.pdf:1532].

Cardiac events captured on Holter monitoring were categorized into atrioventricular (AV) block, supraventricular, and ventricular. Atrioventricular block included first degree, second degree (type 1 and 2), and third degree. Supraventricular events included (but were not limited to) sinus bradycardia, sinus pause, supraventricular tachycardia (SVT), atrial fibrillation (defined as continuous/intermittent on Holter report only, not in data set), and atrial flutter (defined as continuous/intermittent on Holter report only, not in data set). Ventricular events included, but were not limited to accelerated idioventricular rhythm (AIVR)/idioventricular rhythm (IVR) and ventricular tachycardia (VT).

Baseline Holter ECG evaluations were recorded, prior to the first dose of double-blind study medication. Baseline cardiac events were the events captured prior to the first dose of double-blind study medication. On-therapy Holter ECG evaluations were those obtained after the first dose of double-blind study medication through one day after the last dose of double-blind study medication. On-therapy cardiac events were those events with an onset date after the date of the first dose of double-blind study medication through one day after the last dose of double-blind study medication. A post-therapy Holter ECG evaluation was defined as any reading started at least two days after the last dose of double-blind study medication. A post therapy cardiac event was defined as any event with an onset date at least two days after the last dose of double-blind study medication [clinstat\168.pdf:1530-1].

The following table summarizes the new-onset cardiac events, by treatment group, and presents selected odds ratios between groups. Accelerated idioventricular rhythm/idioventricular rhythm, atrial fibrillation, atrial flutter, Mobitz Type I 2nd degree AV block, sinus bradycardia and ventricular tachycardia were all more frequently found in the SB 207499 group than in the placebo group. These findings were echoed by an analysis of the FDA population (not shown but includes asthma patients), in addition to which, supraventricular tachycardia was added as more frequent in the SB 207499 group [clinstat\168.pdf:1558-9]. The strongest outcome variables for both of these populations were the more frequent findings of AIVR/IVR and sinus bradycardia in the SB 207499 group, a mechanistically contradictory set of events.

NDA #21573 (12/24/02, N-000) ISS: FREQUENCY OF TREATMENT-EMERGENT NEW-ONSET CARDIAC EVENTS BASED ON 24-HOUR HOLTER MONITORING FOR PATIENTS WITH COPD IN PHASE 3 STUDIES THAT HAD AT LEAST ONE ON-THERAPY HOLTER [clinstat\168.pdf:1558]√

Cardiac Event	Treatment	Not Present Pre-Therapy N	New Onset n (%)	Odds Ratio	95% CI
AIVR/IVR*	Placebo	141	3 (2.1)		
	SB 207499	269	9 (3.3)	1.592	0.424 - 5.978
atrial fibrillation	Placebo	142	0		
	SB 207499	280	2 (0.7)		
atrial flutter	Placebo	143	0		
	SB 207499	281	1 (0.4)		
1° AV block	Placebo	139	5 (3.6)		
	SB 207499	275	6 (2.2)	0.598	0.179 - 1.994
2° AV block, Mobitz Type I	Placebo	142	0		
	SB 207499	279	2 (0.7)		
2° AV block, Mobitz Type II	Placebo	143	2 (1.4)		
	SB 207499	283	1 (0.4)	0.250	0.022 - 2.781
sinus bradycardia	Placebo	98	12 (12.2)		
	SB 207499	192	29 (15.1)	1.319	0.643 - 2.706
sinus pause	Placebo	140	6 (4.3)		
	SB 207499	273	4 (1.5)	0.332	0.092 - 1.197
supraventricular tachycardia	Placebo	62	29 (46.8)		
	SB 207499	143	65 (45.5)	0.950	0.518 - 1.741
ventricular tachycardia	Placebo	132	11 (8.3)		
	SB 207499	263	23 (8.7)	1.054	0.497 - 2.234

N = total number of patients with at least one on-therapy Holter
Percentages for each finding are based on the number of patients with the specific finding absent pre-therapy.
Odds Ratio is based on SB 207499 divided by placebo.
Each distinct patient is counted once per finding.
* AIVR/IVR = Accelerated Idioventricular Rhythm/Idioventricular Rhythm

II.C. ALL UNCONTROLLED TRIALS

Long-term safety was assessed in Studies 040 and 041. Each study was a multicenter, Phase III, open-label extension study in patients with COPD. Patients completing study 042 or 091 according to the protocol were eligible for entry into Study 040, and patients completing Study 039 were eligible for entry into Study 041. Patients in 041 were given 15mg twice daily and were required to attend the clinic after one, two, and four weeks and then at four-week intervals during the duration of the study. Patients in 040 were given 15mg twice daily and were required to attend the clinic after one, two, and four weeks intervals until week 48 and then at twelve-week intervals for the duration of the study. The studies were ongoing as of 15 March 2002 (cutoff date for interim report). These studies will continue until SB 207499 is approved or the studies are terminated by GlaxoSmithKline [clinstat\iss\iss.pdf:343-4, clinstat\040.pdf:3, clinstat\041.pdf:3].

.. Uncontrolled clinical trials consisted of 1078 patients enrolled in studies 040 and 041, the long-term extensions (LTEs) [clinstat\iss\iss.pdf:344-5]. Patients who fulfilled the following criteria were eligible for inclusion in Studies 040 and 041:

- Males or females with COPD who had completed Study 039, 042, or 091 where patients received SB 207499 15mg twice daily or placebo for 24 weeks, (Study 0039, 042) or 26 weeks (Study 091), without tolerability problems.
- Patients who had given their written informed consent to participate.

Patients who fulfilled any of the following criteria were not eligible for inclusion in Studies 040 and 041:

- Patients who had withdrawn from Study 039, 042, or 092 for any reason.
- Patients who had a positive FOB test between Weeks 20 and 24 in Study 039, 042, or 091.

Deaths and SAEs that occurred between 15 March 2002 and the safety cut-off date of 05 September 2002 are presented for Studies 040 and 041. It should be noted that the baseline characteristics of the patients enrolled into the uncontrolled studies are the baseline characteristics at entry into the respective feeder studies (i.e., Studies 042 and 091 for Study 040, and Study 039 for Study 041).

The primary objective for each study was to evaluate the long-term safety and tolerability of SB 207499 administered at a dosage of 15mg twice daily in patients with COPD. Secondary objectives included further efficacy evaluations of SB 207499 in terms of pulmonary function, disease symptoms, and quality of life. Enrollment in the uncontrolled studies was 723 for Study 040 and 355 for Study 041.

One tablet of SB 207499 15mg was taken twice daily, immediately after breakfast and after the evening meal, in order to improve gastrointestinal tolerability. Concomitant on-demand inhaled beta2-agonists and anticholinergic medication were permitted throughout each study and where possible stable doses were to be administered. All other COPD medications with the exception of theophylline and aminophylline (oral and intravenous) were permitted without restriction during the studies [clinstat\iss\iss.pdf:343-4]. The 120-day safety update added a very few new outcomes only to the information on deaths and serious adverse events in studies 040 and 041. No integration of the new and old information was offered seriously limiting the possible ways in which the new information could be presented. Therefore, the new information will not be included in this section [1/24/03 update\120 day safety update.pdf:147-9].

II.C.1. DEMOGRAPHICS

The demographic characteristics were dictated by the inclusion/exclusion criteria of the feeder studies and were representative of the study population. Patients in the prior placebo group had slightly higher baseline pulmonary function tests at entry into the uncontrolled studies than patients in the prior SB 207499 group. As was true of the feeder studies, these were trials of male Caucasians.

NDA #21573 (12/24/02, N-000) ISS: KEY DEMOGRAPHIC AND PULMONARY CHARACTERISTICS AT SCREENING FOR COPD PATIENTS IN ALL UNCONTROLLED STUDIES [clinstat\iss\iss.pdf:345-6]√		
Demographic Characteristics	**Prior Treatments**	
	Placebo 0 mg bid (N = 383) n (%)	**SB 207499 15 mg bid (N = 695) n (%)**
SEX		
female	78 (20.4)	161 (23.2)
male	305 (79.6)	534 (76.8)
RACE		
white	374 (97.7)	670 (96.4)
black	2 (0.5)	12 (1.7)
other[a]	7 (1.8)	13 (1.9)
AGE (years)		
< 65	180 (47.0)	339 (48.8)
≥ 65	203 (53.0)	356 (51.2)
mean (SD)	64.0 (8.9)	63.4 (9.0)
range	39.0 - 84.0	39.0 - 82.0
WEIGHT (kg)		
mean (SD)	75.9 (15.8)	76.3 (15.8)
range	37.2 - 139.7	38.6 - 140.6
SMOKING STATUS		
current	169 (44.1)	309 (44.5)
previous	214 (55.9)	386 (55.5)
PFTs & SMOKING	**Mean (SD)**	**Mean (SD)**
$FEV_{1.0}$	1.51 (0.50)	1.47 (0.46)
% predicted $FEV_{1.0}$	49.94 (11.69)	49.43 (11.83)
pack-years	48.4 (25.9)	50.3 (28.0)
[a] = This category includes Asian, Hispanic, Oriental and other races.		

II.C.2. DISPOSITION

A summary of subject accountability, including reasons for study withdrawal, is presented in the table that follows for patients in uncontrolled studies. Overall, a total of 440 of 1078 patients (40.8%) were withdrawn from the uncontrolled studies. The most common reason reported for withdrawal was adverse experience, which occurred in 18.3% of all patients. A similar number of patients (17.7%) withdrew due to various reasons grouped under the "Other" category. Only 25 patients (2.3%) had completed the long term uncontrolled studies at the time of data cut-off. Completed patients were from Study 040 Norwegian sites that did not receive approval to extend the study past 2 years [clinstat\iss\iss.pdf:346-7].

NDA #21573 (12/24/02, N-000) ISS: SUMMARY OF PATIENT ACCOUNTABILITY FOR COPD PATIENTS IN ALL UNCONTROLLED STUDIES, THE ITT POPULATION [clinstat\iss\iss.pdf:347]√			
Reason For Withdrawal	**Prior Treatment**		
	Placebo 0 mg bid (N = 383) n (%)	**SB 207499 15 mg bid (N = 695) n (%)**	**Total (N = 1078) n (%)**
adverse event[a]	93 (24.3)	104 (15.0)	197 (18.3)

NDA #21573 (12/24/02, N-000) ISS: SUMMARY OF PATIENT ACCOUNTABILITY FOR COPD PATIENTS IN ALL UNCONTROLLED STUDIES, THE ITT POPULATION [clinstat\iss\iss.pdf:347]√			
	Prior Treatment		
Reason For Withdrawal	Placebo 0 mg bid (N = 383) n (%)	SB 207499 15 mg bid (N = 695) n (%)	Total (N = 1078) n (%)
COPD exacerbation[b]	6 (1.6)	11 (1.6)	17 (1.6)
not due to COPD exacerbation	87 (22.7)	93 (13.4)	180 (16.7)
insufficient efficacy	4 (1.0)	18 (2.6)	22 (2.0)
protocol deviation[c]	8 (2.1)	6 (0.9)	14 (1.3)
lost to follow-up	5 (1.3)	11 (1.6)	16 (1.5)
other	67 (17.5)	124 (17.8)	191 (17.7)
total withdrawn	177 (46.2)	263 (37.8)	440 (40.8)
completed study	10 (2.6)	15 (2.2)	25 (2.3)
bid = *bis in deum* = twice daily [a] = This row includes patients withdrawn due to COPD exacerbations. [b] = Does not apply for patients enrolled into the asthma studies. [c] = This row includes those who were withdrawn for non-compliance.			

II.C.3. EXTENT OF EXPOSURE

The extent of exposure to study medication for patients enrolled in the uncontrolled studies, including and excluding their exposure during the feeder studies, is summarized in the following table. Mean exposure among patients treated with SB 207499 15mg bid in the feeder studies and in the uncontrolled studies was 812.5 days. Patients previously treated with placebo had lower mean days of exposure than patients previously treated with SB 207499, excluding their exposure during the feeder studies (556.4 days for placebo and 638.6 days for SB 207499 15mg bid). The median days of exposure was also lower for patients previously treated with placebo compared to patients previously treated with SB 207499 15mg bid, excluding their exposure during the feeder studies (714 days for placebo and 760 days for SB 207499) [clinstat\iss\iss.pdf:347-8].

NDA #21573 (12/24/02, N-000) ISS: DURATION OF EXPOSURE FOR COPD PATIENTS IN ALL UNCONTROLLED STUDIES [clinstat\iss\iss.pdf:347]√			
	Prior Treatment		
Exposure[a] (days)	Placebo 0 mg bid (N = 383) n (%)	SB 207499	
		15 mg bid[b] (N = 695) n (%)	15 mg bid[c] (N = 695) n (%)
1	383 (100.0)	695 (100.0)	695 (100.0)
> 1	379 (99.0)	695 (100.0)	692 (99.6)
≥ 14	353 (92.2)	695 (100.0)	673 (96.8)
≥ 28	338 (88.3)	695 (100.0)	664 (95.5)
≥ 60	323 (84.3)	695 (100.0)	646 (92.9)
≥ 90	308 (80.4)	695 (100.0)	634 (91.2)
≥ 180	288 (75.2)	685 (98.6)	603 (86.8)
≥ 360	263 (68.7)	602 (86.6)	555 (79.9)
≥ 540	235 (61.4)	539 (77.6)	482 (69.4)
mean (SD)	556.4 (342.7)	812.5 (293.3)	638.6 (293.9)

NDA #21573 (12/24/02, N-000) ISS: DURATION OF EXPOSURE FOR COPD PATIENTS IN ALL UNCONTROLLED STUDIES [clinstat\iss\iss.pdf:347]√			
Exposure[a] (days)	Prior Treatment		
	Placebo 0 mg bid (N = 383) n (%)	SB 207499	
		15 mg bid[b] (N = 695) n (%)	15 mg bid[c] (N = 695) n (%)
median	714	939	760
range	1 - 996	164 - 1179	1 - 996

bid = *bis in deum* = twice daily

[a] = Calculation of exposure: (date of last dose) - (date of first dose) + 1

[b] = Includes exposure during feeder studies.

[c] = Excludes exposure during feeder studies.

II.C.4. ADVERSE EVENTS (AES)

The methods for collection and analysis of adverse experiences in the long-term, uncontrolled extension studies (i.e., Study 040 and Study 041) were essentially the same as those used for the controlled Phase II/III Clinical Studies. Adverse experiences were elicited by the Investigator asking the subject a non-leading question such as "Have you felt different in any way since starting the new treatment or since the last visit?" In order to help the subject to remember and to answer this question accurately, a diary card was provided with space in which the subject could record if they felt different since starting the study medication. The numbers (%) of these patients with the most frequently reported on-therapy AEs, as defined by occurring in ≥ 5% of patients in either prior treatment group, are summarized in study in the following table [clinstat\040.pdf:33, clinstat\041.pdf:47, clinstat\iss\iss.pdf:348]. The abdominal complaints of vomiting, dyspepsia, nausea, abdominal pain and diarrhea (capitalized in the following table) were all less frequent in patients who had prior treatment with SB 207499. Perhaps those patients who previously received SB 207499 and were able remain on it for the duration of the feeder studies were not as susceptible to the abdominal complaints as those whose first exposure to SB 207499 was in the uncontrolled studies. Somewhat curiously, patients who had previously received SB 207499 also had more frequent AEs that were chronic obstructive airways disease and respiratory disorder. This is exactly the reverse of what one would expect from an effective treatment of COPD unless a selection bias for that prior treatment-group in the uncontrolled trials or tachyphylaxis had occurred.

NDA #21573 (12/24/02, N-000) ISS: NUMBER (%) OF PATIENTS WITH THE MOST FREQUENTLY REPORTED ADVERSE EXPERIENCES (≥ 5% IN EITHER PRIOR TREATMENT GROUP) IN ALL UNCONTROLLED STUDIES [clinstat\iss\iss.pdf:348-9]√			
Adverse Experience (Preferred Term)	Prior Treatment Group		TOTAL (N = 1078) n (%)
	Placebo (N = 383) n (%)	SB 3207499 15 mg BID (N = 695) n (%)	
Total[a]	359 (93.7)	650 (96.5)	1009 (93.6)
chronic obstructive airways disease	206 (53.8)	447 (64.3)	653 (60.6)
upper respiratory tract infection	59 (15.4)	128 (18.4)	187 (17.3)
DIARRHEA	85 (22.2)	90 (12.9)	175 (16.2)
ABDOMINAL PAIN	77 (20.1)	96 (13.8)	173 (16.0)

NDA #21573 (12/24/02, N-000) ISS: NUMBER (%) OF PATIENTS WITH THE MOST FREQUENTLY REPORTED ADVERSE EXPERIENCES (≥ 5% IN EITHER PRIOR TREATMENT GROUP) IN ALL UNCONTROLLED STUDIES [clinstat\iss\iss.pdf:348-9]√			
Adverse Experience (Preferred Term)	Prior Treatment Group		TOTAL (N = 1078) n (%)
	Placebo (N = 383) n (%)	SB 3207499 15 mg BID (N = 695) n (%)	
injury	44 (11.5)	98 (14.1)	142 (13.2)
NAUSEA	71 (18.5)	69 (9.9)	140 (13.0)
headache	54 (14.1)	66 (9.5)	120 (11.1)
back pain	32 (8.4)	85 (12.2)	117 (10.9)
DYSPEPSIA	50 (13.1)	64 (9.2)	114 (10.6)
rhinitis	41 (10.7)	73 (10.5)	114 (10.6)
infection viral	35 (9.1)	61 (8.8)	96 (8.9)
coughing	26 (6.8)	57 (8.2)	83 (7.7)
pharyngitis	22 (5.7)	60 (8.6)	82 (7.6)
arthralgia	30 (7.8)	47 (6.8)	77 (7.1)
chest pain	28 (7.3)	45 (6.5)	73 (6.8)
sinusitis	25 (6.5)	48 (6.9)	73 (6.8)
insomnia	21 (5.5)	49 (7.1)	70 (6.5)
respiratory disorder	15 (3.9)	55 (7.9)	68 (6.3)
urinary tract infection	17 (4.4)	50 (7.2)	67 (6.2)
VOMITING	28 (7.3)	38 (5.5)	66 (6.1)
hypertension	18 (4.7)	44 (6.3)	63 (5.8)
dyspnea	22 (5.7)	39 (5.6)	61 (5.7)
dizziness	20 (5.2)	40 (5.8)	60 (5.6)
bronchitis	22 (5.7)	34 (4.9)	56 (5.2)
pain	16 (4.2)	37 (5.3)	53 (4.9)
pneumonia	20 (5.2)	33 (4.7)	53 (4.9)
hyperglycemia	13 (3.4)	37 (5.3)	50 (4.6)
anxiety	22 (5.7)	25 (3.6)	47 (4.4)
arthritis	19 (5.0)	27 (3.9)	46 (4.2)
myalgia	22 (5.7)	23 (3.3)	45 (4.2)
BID = *bis in deum* = twice daily [a] = Total represents total number of patients reporting at least one adverse experience.			

II.C.5. DEATHS

Twenty four patients died during treatment with SB 207499 (8 patients) or after discontinuing treatment (16 patients). The 24 patients are listed and all of the deaths were attributed to adverse events judged not related or unlikely related to study medication [clinstat\iss\iss.pdf:361-2]. The most striking finding in this table is the relatively few female deaths (2/24 = 8.3%) compared with the demographics of female gender participation (22.2%) in all uncontrolled trials [clinstat\iss\iss.pdf:345].

NDA #21573 (12/24/02, N-000) ISS: PATIENT DEATHS FOR COPD PATIENTS IN ALL UNCONTROLLED STUDIES [clinstat\iss\iss.pdf:362-3]√						
Patient ID	Age (yrs)	Gender	Days On/After[a]	Cause	Fatal SAE[b]	Related
ON-THERAPY: SB 207499 (15 mg twice daily)						
040.210.07343	66	male	76/1	COPD exacerbation	Chronic Obstructive Airways Disease	Not
040.250.08152	59	male	260/1	CHF	cardiac failure	Not

NDA #21573 (12/24/02, N-000) ISS: PATIENT DEATHS FOR COPD PATIENTS IN ALL UNCONTROLLED STUDIES [clinstat\iss\iss.pdf:362-3]√						
Patient ID	**Age (yrs)**	**Gender**	**Days On/After[a]**	**Cause**	**Fatal SAE[b]**	**Related**
040.257.08167	56	male	145/1	bronchopneumonia	pneumonia	Unlikely
040.343.07559	74	male	111/1	death by hanging	suicide attempt	Not
041.038.05052	77	male	335/0	heart failure	cardiac failure	Not
041.053.05632	75	male	170/0	MI	MI	Not
041.078.06359	70	male	282/0	probable MI	MI	Unlikely
041.207.06207	68	male	668/0	MI	MI	Unlikely
POST-THERAPY (after discontinuing treatment with SB 207499)						
040.101.09693	66	female	364/11	COPD	Chronic Obstructive Airways Disease	Unlikely
040.103.10638	66	male	97/5	pneumonia pulmonary	pneumonia	Not
040.105.09275	69	male	727/55	respiratory insufficiency	respiratory insufficiency	Not
040.153.10861	84	male	508/7	CHF & respiratory failure	Chronic Obstructive Airways Disease	Not
040.164.09439	73	male	140/92	final cardio-respiratory failure	cardiac arrest	Not
040.181.10339	76	male	329/28	multi-organ failure	circulatory failure	Not
040.217.14181	71	male	781/17	pulmonary arrest	cardiac arrest	Not
040.218.07119	71	male	640/59	secondary hematuria	neoplasm NOS	Unlikely
040.220.07105	63	male	905/58	respiratory arrest	cardiac arrest	Not
040.221.07679	69	male	677/28	cardiac arrest	cardiac arrest	Not
040.241.07546	56	male	608/98	MI	sudden death	Unlikely
040.241.07530	51	female	627/8	metastatic liver disease	neoplasm malignant	Unlikely
040.250.08071	75	male	593/117	bronchopneumonia	pneumonia	Not
040.338.08293	74	male	495/6	MI	MI	Not
041.092.06492	74	male	110/61	cardiac arrest/CAD	cardiac arrest	Unlikely
040.358.08252	73	male	557/7	cardiac failure due to COPD exacerbation	Chronic Obstructive Airways Disease	Not

[a] = days on randomized medication/days post study
[b] = preferred term

II.C.6. SERIOUS ADVERSE EVENTS (SAES)

Two hundred seventy-three patients (25.3% of the 1078 enrolled patients) had one or more SAEs during the uncontrolled studies. Nearly all SAEs were events that are commonly observed in a population of older patients. The numbers and patterns of SAEs did not differ by prior treatment. SAEs of gastrointestinal bleeding occurred in seven SB 207499 treated patients (040.181.10339, 040.214.07176, 040.218.07116 & 041.040.06611-GI hemorrhage; 040.241.07622-hematemsis; 040.152.09559 & 040.163.09546-hemorrhoids) [clinstat\iss\iss.pdf:364].

NDA #21573 (12/24/02, N-000) ISS: NUMBER (%) OF PATIENTS WITH THE MOST FREQUENTLY (≥ 1% OF PATIENTS IN ANY TREATMENT GROUP) REPORTED SERIOUS ADVERSE EVENTS FOR COPD PATIENTS IN ALL UNCONTROLLED STUDIES [clinstat\iss\iss.pdf:364]√			
Adverse Experience (preferred term)	Prior Treatment		Total (N = 1078) n (%)
	Placebo (N = 383) n (%)	SB 207499 15 mg BID (N = 695) n (%)	
Total	95 (24.8)	178 (25.6)	273 (25.3)
Chronic Obstructive Airways Disease	30 (7.8)	55 (7.9)	85 (7.9)
pneumonia	13 (3.4)	21 (3.0)	34 (3.2)
injury	2 (0.5)	18 (2.6)	20 (1.9)
chest pain	4 (1.0)	9 (1.3)	13 (1.2)
angina pectoris	4 (1.0)	6 (0.9)	10 (0.9)
pulmonary carcinoma	1 (0.3)	9 (1.3)	10 (0.9)
myocardial infarction	6 (1.6)	.3 (0.4)	9 (0.8)
neoplasm NOS	4 (1.0)	5 (0.7)	9 (0.8)
abdominal pain	4 (1.0)	2 (0.3)	6 (0.1)
BID = *bis in deum* = twice daily			

II.C.7. WITHDRAWALS DUE TO ADVERSE EVENTS

There were twice as many withdrawals due to adverse events in patients previously treated with placebo than with SB 207499. The withdrawals due to adverse events in the uncontrolled trials for GI adverse events (capitalized in the table below) also were more frequent in patients previously treated with placebo than with SB 207499. This latter observation is a repetition of the same finding for all adverse events and for all serious adverse events in these uncontrolled trials [clinstat\iss\iss.pdf:365-6].

NDA #21573 (12/24/02, N-000) ISS: NUMBER (%) OF PATIENTS WITH THE MOST FREQUENTLY (> 2 PATIENTS IN BOTH TREATMENT GROUPS) REPORTED FOR COPD PATIENTS IN ALL UNCONTROLLED STUDIES [clinstat\iss\iss.pdf:365-6]√			
Adverse Experience (preferred term)	Prior Treatment		Total (N = 1078) n (%)
	Placebo (N = 383) n (%)	SB 207499 15 mg BID (N = 695) n (%)	
Total	88 (23.0)	89 (12.8)	177 (16.4)
ABDOMINAL PAIN	23 (6.0)	13 (1.9)	36 (3.3)
NAUSEA	22 (5.7)	4 (0.6)	26 (2.4)
DIARRHEA	16 (4.2)	7 (1.0)	23 (2.1)
chronic obstructive airways disease	6 (1.6)	11 (1.6)	17 (1.6)
VOMITING	10 (2.6)	2 (0.3)	12 (1.1)
pulmonary carcinoma	1 (0.3)	8 (1.2)	9 (0.8)
headache	3 (0.8)	2 (0.3)	5 (0.5)
myocardial infarction	3 (0.8)	2 (0.3)	5 (0.5)
pneumonia	2 (0.5)	3 (0.4)	5 (0.5)
cardiac failure	2 (0.5)	2 (0.3)	4 (0.4)
DYSPEPSIA	3 (0.8)	1 (0.1)	4 (0.4)
angina pectoris	1 (0.3)	2 (0.3)	3 (0.3)
anxiety	2 (0.5)	1 (0.1)	3 (0.3)
carcinoma	1 (0.3)	2 (0.3)	3 (0.3)
dizziness	1 (0.3)	2 (0.3)	3 (0.3)
fibrillation atrial	1 (0.3)	2 (0.3)	3 (0.3)

NDA #21573 (12/24/02, N-000) ISS: NUMBER (%) OF PATIENTS WITH THE MOST FREQUENTLY (> 2 PATIENTS IN BOTH TREATMENT GROUPS) REPORTED FOR COPD PATIENTS IN ALL UNCONTROLLED STUDIES [clinstat\iss\iss.pdf:365-6]√			
	Prior Treatment		
Adverse Experience (preferred term)	Placebo (N = 383) n (%)	SB 207499 15 mg BID (N = 695) n (%)	Total (N = 1078) n (%)
BID = *bis in deum* = twice daily			

II.C.8. GASTROINTESTINAL ADVERSE EVENTS OF CONCERN

The numbers (%) of patients with the most frequently reported on-therapy GIAEs of concern in the uncontrolled studies, as defined by occurring in ≥0.5% of patients in either prior treatment group, totaled 141 (13.1%) of patients out of 1078 total patients. Though it is relatively unimportant, more patients treated with placebo (18.0%) in the feeder studies suffered GIAEs of concern than did patients previously treated with SB 207499 (10.4%) [clinstat\iss\iss.pdf:352]. This lower reporting of GIAEs by completers of feeder studies who had received SB 207499 than placebo has been also noted with AEs and withdrawals because of AEs in these uncontrolled trials.

Of these 141 patients with GIAEs of concern, 68 (48.2%) patients had a FOB test performed within 14 days of the target event and 8 of these were positive. Only 3 of these FOB-positive patients ever had a colonoscopy, patients #3, #7 and #9 on the colonoscopy list that follows the next paragraph [clinstat\iss\iss.pdf:354-5]. A total of 80 patients of the 141 had accompanying orthostatic vital signs "of concern" and 3 of these had heart rate changes of "high concern" [clinstat\iss\iss.pdf:353, 11892-3].

Our interest in GIAEs of potential concern lies in establishing the safety of SB 207499 specifically with regard to ruling out mesenteric arteritis. This was a preclinical finding that limited dose escalation. Thirteen patients who were in both treatment groups in feeder studies, entered the uncontrolled long-term extensions, Studies 40 and 41, where they received SB 207499, had a GIAE of concern and underwent colonoscopies because it was felt that the procedures were clinically indicated. Narratives of these colonoscopy reports follow and none reported lesions consistent with mesenteric arteritis [clinstat\iss\iss.pdf:354-5].

1. Patient 040.102.9281 (prior placebo group) with a GIAE of concern of melena (day 564 and 569, 4 and 11 April 2001 respectively) had a colonoscopy performed (20 Jul 2001) that revealed polyps. The FOB result at the time of the GIAE of concern was negative.

2. Patient 040.101.9297 (prior SB207499 group) with a GIAE of concern of melena (day 580, 16 March 2001) had a colonoscopy performed (21-Mar 2001) that revealed hyperplastic polyps.

3. Patient 040.148.9866 (prior SB207499 group) with a GIAE of concern of neoplasm not otherwise specified (NOS) (day 850, 17 Nov-01) had a colonoscopy performed (26-Nov-01) that revealed polyps. The FOB result at the time of the GIAE of concern was positive.

4. Patient 040.162.9354 (prior SB207499 group) with a GIAE of concern of melena (day 404 7 Nov-2000) had a colonoscopy performed that revealed polyps (21-Nov-2000).

5. Patient 040.181.10339 (prior placebo group) experienced a GIAE of concern of hemorrhage (day 192, 26 August 2000) had an endoscopy and colonoscopy performed on 26 August 2000. These revealed no findings. This subject continued on therapy without recurrence of the problem.

6. Patient 040.295.7226 (prior SB207499 group) with a GIAE of concern hemorrhoids (day 462 9 Jan-01) had a colonoscopy performed (22-Feb-01) that revealed grade I hemorrhoids.

7. Patient 040.226.7371 (prior SB207499 group) with a GIAE of concern of gastroenteritis (day 237 and tenesmus day 540, 24-Jan –01 had a colonoscopy performed (15-mar-01) that revealed isolated diverticula and loss of haustration in the descending colon without mucosal lesions. The FOB result at the time of the GIAE of concern was positive.

8. Patient 041.013.05604 (prior placebo group) experienced a GIAE of concern (abdominal pain) on Day 51. An abdominal/pelvic CT scan was performed on Day 62 (03 Nov 1999), with no remarkable findings and a colonoscopy was performed on Day 76 (17 Nov 1999) with a finding of diverticular disease. No other abnormalities were noted. All FOB tests for this patient were negative.

9. Patient 041.020.05598 (prior SB 207499 group) experienced GIAEs of concern (abdominal pain and hemorrhoids) on Days 301, 302, 732, and 738. The patient had a positive FOB test on Day 303, and all other FOB tests were negative. A colonoscopy was performed on Day 329 (04 Aug 2000). The colonoscopy confirmed hemorrhoids, but was otherwise normal. A CAT scan was performed on Day 739 (17 Sept 2001) with findings of gallstones and a cyst in the right kidney.

10. Patient 041.038.05057 (prior SB 207499 group) experienced a GIAE of concern (melena) on Day 232. The patient also had subsequent positive FOB tests on Days 333, 362, and 363. A colonoscopy was performed on Day 321 (19 Jun 2000). This procedure showed hemorrhoids, but no other abnormalities were found.

11. Patient 041.058.05316 (prior SB 207499 group) experienced the following GIAEs of concern: constipation, Day 119; melena, Day 120; and hemorrhoids, Day 140. On Day 159 (31 Jan 2000) a sigmoidoscopy was performed that revealed rectal bleeding

and polyps. A colonoscopy was performed on Day 176 (17 Feb 2000). The procedure showed two small colon polyps and hemorrhoids, but was otherwise normal.

12. Patient 041.062.05509 (prior placebo group) experienced serious GIAEs of concern (diverticulitis, gastritis, neoplasm NOS, and anemia) on Day 465. A colonoscopy was performed on Day 467 (27 Nov 2000). The colonoscopy showed multiple colonic polyps, right and left-sided diverticulosis, and hemorrhoids.

13. Patient 041.064.06001 (prior placebo group) experienced a post-therapy GIAE of concern (Day 701, 5 days after withdrawal). A colonoscopy was performed on Day 819 (06 Feb 2002) with no abnormal findings. FOB test results for the patient were positive on Days 728 and 729, but were subsequently negative at follow-up.

In Study 041 a total of 26 patients who did not report GIAEs of concern had colonoscopies or other GI procedures performed. Of these 26 patients, 11 patients with on-therapy AEs of the gastrointestinal system (not reported as GIAEs of concern) had colonoscopies performed. Brief narratives for these 11 patients are provided below and there were no reported findings consistent with mesenteric arteritis [clinstat\iss\iss.pdf:355-8].

1. Patient 041.006.05480 experienced AEs of abdominal pain and diarrhea of mild intensity on Day 1 that were not reported as GIAEs of concern. The events resolved in one day. The patient also experienced dyspepsia of mild intensity on Day 7 that was not reported as a GIAE of concern. The event resolved in one day. The Investigator considered all three events to be unrelated to study medication. A colonoscopy was performed on Day 64 (05 Oct 1999). The patient was noted to have severe sigmoid diverticulosis with spasm. Two small rectal polyps were removed. Otherwise, the findings were normal. All FOB tests were negative for this patient.

2. Patient 041.014.05166 (prior SB 207499 group) experienced an AE of diverticulitis of mild intensity on Day 944 that was not reported as a GIAE of concern. The event was ongoing. The Investigator considered the event to be unrelated to study medication. A colonoscopy was performed on Day 944 (29 Jan 2002). In the left colon, a single small polyp was removed and the patient was noted to have a mild degree of sigmoid diverticulosis. Otherwise, the findings were normal. All FOB tests were negative for this patient.

3. Patient 041.032.05309 (prior SB 207499 group) experienced an AE of abdominal pain of mild intensity on Day 15 that was not reported as a GIAE of concern. The event resolved in one day. The Investigator considered the event to be unlikely related to study medication. The patient also experienced AEs of abdominal pain of mild intensity and anorexia of moderate intensity on Day 52 that were not reported as GIAEs of concern. The abdominal pain resolved in 121 days, and the anorexia resolved in 130 days. The Investigator considered the latter two AEs to be unrelated

and unlikely related to study medication, respectively. On Day 160 (14 Feb 2000) a CT scan of the abdomen and pelvis was conducted, which demonstrated an incidental finding of a left adrenal cyst as well as nonspecific prostatic enlargement. A colonoscopy and esophagogastroduodenoscopy were performed on Day 170 (24 Feb 2000). Two diminutive hepatic flexure polyps, one diminutive transverse colon polyp, and one rectal polyp were removed. Colonoscopy findings were otherwise normal. The esophagogastroduodenoscopy findings were normal except for antral gastritis. All FOB tests were negative for this patient.

4. Patient 041.037.06606 (prior placebo group) experienced AEs of abdominal pain (Days 102 and 343; mild intensity), diarrhea (Day 343; moderate intensity), dysphagia (Day 344; mild intensity), eructation (Day 7; severe intensity), flatulence (Days 7 and 343; mild to severe intensity), irritable bowel syndrome (Day 538; mild intensity), and stomatitis (Day 148; moderate intensity), that were not reported as GIAEs of concern. The abdominal pain, diarrhea, dysphagia, flatulence, and irritable bowel syndrome were ongoing, while the remaining events resolved in 4 to 5 days. The Investigator considered the events to be unrelated or unlikely related to study medication. A sigmoidoscopy was performed on Day 117 (05 Jun 2000) with findings of hemorrhoids. A colonoscopy was performed on Day 502 (25 Jun 2001) with findings of sigmoid diverticulosis and internal hemorrhoids. An esophagogastroduodenoscopy was also performed on Day 502 with findings of possible gastritis and bland duodenum. All FOB tests were negative for this patient.

5. Patient 041.040.06611 (prior SB 207499 group) experienced SAEs of diverticulitis and GI hemorrhage of severe intensity on Day 683 that were not reported as GIAEs of concern. The events resolved in 7 days. The Investigator considered the events to be unlikely related to study medication. A colonoscopy was performed on Day 606 (25 Sep 2001), however the patient could not tolerate further advancement of the endoscope into the transverse colon. Hemorrhoids and multiple diverticula of the colon were detected. On Day 685 (13 Dec 2001), a colonoscopy showed multiple large diverticula and active bleeding without an obvious source. All FOB tests were negative for this patient.

6. Patient 041.046.05963 (prior SB 207499 group) experienced AEs of abdominal pain (Day 237) and nausea (Day 369). Both events were considered by the Investigator to be moderate and unlikely related to study medication. The abdominal pain resolved in 9 days and the nausea resolved in 1 day. A colonoscopy and endoscopy were performed on Day 778 (28 Feb 2002) with findings of diverticula in the distal colon and a ring at the gastroesophageal junction above a hiatal hernia. All FOB tests were negative for this patient.

7. Patient 041.055.06014 (prior SB 207499 group) experienced an AE of melena (positive hemoccult test) of mild intensity on Day 359 that was not reported as a GIAE of concern. The event was ongoing and the Investigator considered the event to be not related to study medication. A colonoscopy was performed on day 458 (08

Feb 2001) with no neoplastic, inflammatory of vascular changes were noted. Subsequent FOB tests were negative.

8. 041.062.06531 (prior SB207499group) experience an AE of nausea of mild intensity on Day 2 that was not reported as a GIAE of concern that resolved and the Investigator considered the event to be not related to study medication. A colonoscopy and hemorrhoidectomy were performed on day Day 82 (15 May 2000) with findings of a GI bleed from hemorrhoids.

9. Patient 041.069.06505 (prior placebo group) experienced AEs of abdominal pain (Day 9, moderate intensity), diarrhea (Day 2, mild intensity), dyspepsia (Days 26, 30, 51, 63, 74, 84, 108; mild to severe intensity) that were not reported as GIAEs of concern. All of these events resolved in 1 to 5 days. The Investigator considered the events to be unlikely related to study medication. On Day 451, the patient experienced AEs of esophagitis of moderate intensity, gastritis of mild intensity, and gastrointestinal disorder NOS (hiatal hernia) of moderate intensity that were not reported as GIAEs of concern. The events were ongoing, and were considered by the Investigator to be unlikely related to study medication. On Days 433 and 717, the patient experienced AEs of melena of mild intensity that were not reported as GIAEs of concern. The events resolved in 2 days and 37 days, respectively. The Investigator considered the AEs of melena to be unrelated to study medication. On Day 451 (16 Apr 2001), a colonoscopy and an esophagogastroduodenoscopy were performed. The colonoscopy showed mild sigmoid diverticulosis, and the esophagogastroduodenoscopy detected moderate esophagitis, a mild hiatal hernia, and mild gastritis, but the findings were otherwise normal. FOB tests results were positive for the patient on Day 717, but were otherwise negative.

10. Patient 041.073.06499 (prior SB 207499 group) experienced an AE of neoplasm NOS (benign colon polyps) of moderate intensity on Day 256 that was not reported as a GIAE of concern. The event resolved in 1 day. The Investigator considered the event to be unrelated to study medication. On Day 256 (18 Sep 2000), a colonoscopy was performed. Four benign colon polyps were removed. The procedure also showed diverticula of the sigmoid, descending, and ascending colon. Otherwise, the findings were normal. All FOB tests were negative for this patient.

11. Patient 041.092.06577 (prior placebo group) experienced AEs of vomiting (Day 1), flatulence (Day 8), and nausea (Day 82) of moderate intensity that were not reported as GIAEs of concern. The flatulence and nausea resolved in 1 day and were considered by the Investigator to be unrelated to study medication. The nausea resolved in 26 days and was considered by the Investigator to be probably related to study medication. On Day 133 (22 May 2000), a colonoscopy was performed. Moderate diverticulosis and moderate hemorrhoids were detected. FOB tests results were positive on Days 112 and 113, but were negative at Day 114.

II.C.9. FECAL OCCULT BLOOD

A total of 888 (82.4%) of 1078 patients had FOB tests during the uncontrolled studies. The number (%) of COPD patients with on-therapy FOB results is presented for the uncontrolled studies in the table below. About twice the frequency of prior SB 207499 treated patients, compared with prior placebo treated patients transitioned from negative at baseline to positive sometime during uncontrolled therapy, but the numbers and percentages were small [clinstat\iss\iss.pdf:397, 12722].

NDA #21573 (12/24/02, N-000) ISS: NUMBER AND PERCENTAGE OF COPD PATIENTS WITH ON-THERAPY FECAL OCCULT BLOOD RESULTS IN UNCONTROLLED STUDIES [clinstat\iss\iss.pdf:12722]√

Prior Treatment	Baseline	Number Of Patients Tested	On-Therapy	
			Negative n (%)*	Positive n (%)*
Placebo	negative	291	283 (97.3)	8 (2.7)
	positive	2	2 (100.0)	0
	missing	2	2 (100.0)	0
SB 207499	negative	588	588 (94.9)	30 (5.1)
	positive	2	1 (50.0)	1 (50.0)
	missing	3	3 (100.0)	0

* Percentages are calculated based on the row totals for each treatment.

II.C.10. PREGNANCIES

There were no pregnancies in the long-term uncontrolled trials [clinstat\iss\iss.pdf:366].

II.C.11. LABORATORY DATA IN UNCONTROLLED TRIALS

Transition (shift) tables of numbers of patients who had normal laboratory values at baseline to maximum or minimum values during treatment are presented for hematology and chemistry laboratory values. The criteria of "low concern," "low," "high," and "high concern" have previously been defined [clinstat\iss\iss.pdf:351].

A comparison between patients receiving different treatments during the feeder trials who shifted from normal to lower or higher than normal values during the uncontrolled treatment trials are small, inconsistent and of unknown meaningfulness. Regardless of the feeder treatment, the frequency of shifts to lower-than-normal exceeded the percentage of shifts to higher-than normal for hemoglobin. Exactly the reverse was true for hematocrit, nullifying the importance of these shifts for both variables. Also, regardless of the feeder treatment, larger percentages of shifts to higher-than-normal rather than lower-than-normal values are apparent for all of the remaining variables, WBC, neutrophils, eosinophils and platelets. This may be because these variables are non-specific acute phase reactants, because this is a true drug effect or because their normal ranges are close to zero at the lowest extent of their possible values but relatively unbounded in an upward direction.

NDA #21573 (12/24/02, N-000) ISS: TRANSITIONS FROM NORMAL RANGE AT BASELINE FOR HEMATOLOGY LABORATORY VALUES OF COPD PATIENTS PREVIOUSLY TREATED WITH PLACEBO AND SB 207499 (15 mg TWICE DAILY) IN ALL UNCONTROLLED STUDIES, THE ITT POPULATION [clinstat\iss\iss.pdf:374]√

Variable[a]	N[b]	On-Therapy				
		Low Concern n (%)	Low n (%)	Normal n (%)	High n (%)	High Concern n (%)
HEMOGLOBIN (g/L)						
Placebo	331	5 (1.5)	43 (13.0)	246 (74.3)	40 (12.1)	0
SB 207499 15 mg BID	610	8 (1.3)	96 (15.7)	435 (71.3)	71 (11.6)	1 (0.2)
HEMATOCRIT (%)						
Placebo	309	4 (1.3)	45 (14.6)	190 (61.5)	75 (24.3)	1 (0.3)
SB 207499 15 mg BID	591	5 (0.8)	107 (18.1)	324 (54.8)	161 (27.2)	1 (0.2)
WBC (10^9/L)						
Placebo	339	4 (1.2)	14 (4.1)	226 (66.7)	94 (27.7)	3 (0.9)
SB 207499 15 mg BID	642	8 (1.2)	24 (3.7)	399 (62.1)	205 (31.9)	10 (1.6)
NEUTROPHILS ABSOLUTE (10^9/L)						
Placebo	346	6 (1.7)	13 (3.8)	225 (65.0)	81 (23.4)	23 (6.6)
SB 207499 15 mg BID	648	22 (3.4)	25 (3.9)	395 (61.0)	171 (26.4)	43 (6.6)
EOSINOPHILS ABSOLUTE (10^9/L)						
Placebo	347	0	0	293 (84.4)	51 (14.7)	3 (0.9)
SB 207499 15 mg BID	653	0	0	551 (84.4)	92 (14.1)	10 (1.5)
PLATELET COUNT (10^9/L)						
Placebo	353	7 (2.0)	18 (5.1)	289 (81.9)	25 (7.1)	16 (4.5)
SB 207499 15 mg BID	648	13 (2.0)	27 (4.2)	515 (79.5)	71 (11.0)	26 (4.0)

[a] = For each variable, numbers are listed separately for patients treated with placebo or SB 207499 in the feeder studies.

[b] = Number of patients with values within the normal range at baseline. Percentages are based on the number of patients with values within the normal range at baseline.

BID = *bis in deum* = twice daily

Note: Patients with on-therapy values who meet criteria for both high and low values of interest and concern are reported in both categories, if applicable. Patients are assigned to categories based on their highest and/or lowest on-therapy value.

Patients previously treated with SB 207499 had relatively more shifts to above-normal, compared with placebo, for the clinical chemistries (AST, alkaline phosphatase, sodium and potassium) during the uncontrolled trials. These differences were small and of unknown clinical significance.

NDA #21573 (12/24/02, N-000) ISS: TRANSITIONS FROM NORMAL RANGE AT BASELINE FOR CHEMISTRY LABORATORY VALUES OF COPD PATIENTS PREVIOUSLY TREATED WITH PLACEBO AND SB 207499 (15 mg TWICE DAILY) IN ALL UNCONTROLLED STUDIES [clinstat\iss\iss.pdf:375-6]√

Variable[a]	N[b]	On-Therapy				
		Low Concern n (%)	Low n (%)	Normal n (%)	High n (%)	High Concern n (%)
AST (IU/L)						
Placebo	356	0	0	339 (95.2)	13 (3.7)	4 (1.1)
SB 207499 15 mg BID	668	0	0	607 (90.9)	48 (7.2)	13 (1.9)
ALT (IU/L)						
Placebo	352	0	0	322 (91.5)	28 (8.0)	2 (0.6)
SB 207499 15 mg BID	661	0	0	588 (89.0)	58 (8.8)	15 (2.3)
GGT (IU/L)						

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Variable[a]	N[b]	On-Therapy				
		Low Concern n (%)	Low n (%)	Normal n (%)	High n (%)	High Concern n (%)
Placebo	330	0	0	275 (83.3)	48 (14.5)	7 (2.1)
SB 207499 15 mg BID	596	0	0	509 (85.4)	66 (11.1)	21 (3.5)
TOTAL BILIRUBIN (micromol/L)						
Placebo	359	0	0	324 (90.3)	29 (8.1)	6 (1.7)
SB 207499 15 mg BID	661	0	0	592 (89.6)	59 (8.9)	10 (1.5)
ALKALINE PHOSPHATASE (IU/L)						
Placebo	348	0	0	333 (95.7)	15 (4.3)	0
SB 207499 15 mg BID	653	0	0	603 (92.3)	50 (7.7)	0
CREATININE (micromol/L)						
Placebo	350	1 (0.3)	29 (8.3)	285 (81.4)	35 (10.0)	0
SB 207499 15 mg BID	651	0	68 (10.4)	533 (81.9)	48 (7.4)	3 (0.5)
BUN (mmol/L)						
Placebo	358	0	0	316 (88.3)	42 (11.7)	0
SB 207499 15 mg BID	661	0	0	581 (87.9)	78 (11.8)	2 (0.3)
SODIUM (mmol/L)						
Placebo	349	6 (1.7)	38 (10.9)	244 (69.9)	54 (15.5)	9 (2.6)
SB 207499 15 mg BID	656	13 (2.0)	70 (10.7)	435 (66.3)	127 (19.4)	24 (3.7)
POTASSIUM (mmol/L)						
Placebo	353	2 (0.6)	9 (2.5)	276 (78.2)	14 (4.0)	53 (15.0)
SB 207499 15 mg BID	649	2 (0.3)	24 (3.7)	480 (74.0)	38 (5.9)	105 (16.2)
GLUCOSE, RANDOM (mmol/L)						
Placebo	277	3 (1.1)	42 (15.2)	94 (33.9)	78 (28.2)	88 (31.8)
SB 207499 15 mg BID	518	4 (0.8)	110 (21.2)	175 (33.8)	128 (24.7)	161 (31.1)
URIC ACID (micromol/L)						
Placebo	359	0	0	323 (90.0)	34 (9.5)	2 (0.6)
SB 207499 15 mg BID	657	0	0	599 (91.2)	57 (8.7)	1 (0.2)

[a] = For each variable, numbers are listed separately for patients treated with placebo or SB 207499 in the feeder studies.

[b] = Number or patients with values within the normal range at baseline. Percentages are reported for patients with values within the normal range at baseline.

BID = *bis in deum* = twice daily

Note: Patients with on-therapy values who meet criteria for both high and low values of interest and concern are reported in both categories, if applicable. Patients are assigned to categories based on their highest and/or lowest on-therapy value.

II.C.12. VITAL SIGNS

A comparison between p atients receiving different treatments during the feeder trials who shifted from normal to lower or higher than normal vital sign values during the uncontrolled treatment trials were small, inconsistent and of unknown meaningfulness. Regardless of the feeder treatment, the frequency of shifts to higher-than-normal exceeded the percentage of shifts to lower-than normal for systolic and diastolic blood pressures. Heart rate showed about equal shift frequencies in both directions.

NDA #21573 (12/24/02, N-000) ISS: TRANSITIONS FROM NORMAL RANGE AT BASELINE FOR VITAL SIGNS OF PLACEBO AND SB 207499 (15 mg TWICE DAILY) TREATMENT GROUPS FOR COPD PATIENTS IN ALL UNCONTROLLED STUDIES [clinstat\iss\iss.pdf:379]√						
		On-Therapy[a]				
Variable/Treatment[c]	N[b]	Low Concern n (%)	Low n (%)	Normal n (%)	High n (%)	High Concern n (%)
SITTING SYSTOLIC BP (mm Hg)						
Placebo	216	0	5 (2.3)	79 (36.6)	132 (61.1)	1 (0.5)
SB 207499 15 mg BID	425	0	14 (3.3)	143 (33.6)	268 (63.1)	4 (0.9)
SITTING DIASTOLIC BP (mm Hg)						
Placebo	304	6 (2.0)	37 (12.2)	157 (51.6)	110 (36.2)	1 (0.3)
SB 207499 15 mg BID	578	5 (0.9)	76 (13.1)	276 (47.8)	233 (40.3)	2 (0.3)
HEART RATE (bpm)						
Placebo	340	3 (0.9)	55 (16.2)	199 (58.5)	79 (23.2)	6 (1.8)
SB 207499 15 mg BID	640	11 (1.7)	117 (18.3)	395 (61.7)	119 (18.6)	8 (1.3)

BID = *bis in deum* = twice daily

[a] = Patients who meet criteria for both high and low values of interest and concern are reported in both categories.

[b] = Number and percentages are based on the patients with values within the normal range at baseline.

[c] = Indicates patients assigned to each treatment in the respective feeder study.

II.C.13. CARDIOVASCULAR SAFETY

Transitions from normal range at baseline for trough ECG variables in all uncontrolled trials are shown in the table below [clinstat\iss\iss.pdf:384]. For all electrocardiographic variables, shift from normal to higher than normal exceeded shifts to lower than normal. There didn't seem to be any large or consistent differences in percents of patients in these categories over all variables between the two feeder treatments.

NDA #21573 (12/24/02, N-000) ISS: TRANSITIONS FROM NORMAL RANGE AT BASELINE FOR TROUGH ECG VALUES FOR COPD PATIENTS IN ALL UNCONTROLLED STUDIES [clinstat\iss\iss.pdf:384 5/9/03 clinstat\attachment1.pdf:3]√						
		On-Therapy[a]				
VARIABLE Prior Treatment[c]	N[b]	Low Concern n (%)	Low n (%)	Normal n (%)	High n (%)	High Concern n (%)
ATRIAL RATE (bpm)						
Placebo	331	12 (3.6)	43 (13.0)	201 (60.7)	69 (20.8)	13 (3.9)
SB 207499 15 mg BID	609	21 (3.4)	80 (13.1)	373 (61.2)	123 (20.2)	19 (3.1)
VENTRICULAR RATE (bpm)						
Placebo	331	14 (4.2)	42 (12.7)	200 (60.4)	71 (21.5)	11 (3.3)
SB 207499 15 mg BID	311	21 (3.4)	81 (13.3)	376 (61.5)	125 (20.5)	15 (2.5)
QRS DURATION (msec)						
Placebo	335	0	0	311 (92.8)	24 (7.2)	0
SB 207499 15 mg BID	643	0	0	592 (92.1)	51 (7.9)	0
PR INTERVAL (msec)						
Placebo	333	0	0	302 (90.7)	31 (9.3)	0
SB 207499 15 mg BID	615	0	0	541 (88.0)	72 (11.7)	2 (0.3)
QTc INTERVAL (msec)[c]						
Placebo	262	0	0	120 (45.8)	93 (35.5)	49 (18.7)
SB 207499 15 mg BID	483	0	0	220 (45.5)	169 (35.0)	94 (19.5)

NDA #21573 (12/24/02, N-000) ISS: TRANSITIONS FROM NORMAL RANGE AT BASELINE FOR TROUGH ECG VALUES FOR COPD PATIENTS IN ALL UNCONTROLLED STUDIES [clinstat\iss\iss.pdf:384 5/9/03 clinstat\attachment1.pdf:3]√

VARIABLE Prior Treatment[c]	N[b]	On-Therapy[a]				
		Low Concern n (%)	Low n (%)	Normal n (%)	High n (%)	High Concern n (%)
QT INTERVAL (msec)						
Placebo	362	NA	NA	357 (98.6)	NA	5 (1.4)
SB 207499 15 mg BID	676	NA	NA	666 (98.5)	NA	10 (1.5)
QTc CHANGE FROM BASELINE (msec)[d]						
Placebo	262	0	0	173 (66.0)	77 (29.4)	12 (4.6)
SB 207499 15 mg BID	483	0	0	326 (67.5)	130 (26.9)	27 (5.6)

[a] = Patients are assigned to categories based on their highest and/or lowest on-therapy value. Patients with on-therapy values who meet criteria for both high and low values of interest and concern are reported in both categories, if applicable.

[b] = Number of patients with values within the normal range at baseline. Percentages are based on the number of patients with values within the normal range at baseline.

[c] = QT corrected by Bazett's formula.

[d] = Number of patients with values within the normal range at baseline. Percentages are based on the number of patients with values within the normal range at baseline.

NA = Not Applicable

BID = *bis in deum* = twice daily

Number (%) of patients with the most frequently reported new-onset ECG abnormalities (≥ 1% of patients in any prior treatment group) in the uncontrolled studies were presented. The identity of the prior feeder treatment did not seem to be related to any differences in the frequencies of the ECG abnormalities [clinstat\iss\iss.pdf:385].

III. APPENDIX

III.A. STUDY CPMS-039

A Randomized, 24-week, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Ariflo (SB 207499, 15 mg Twice Daily) in Patients with Chronic Obstructive Pulmonary Disease (COPD)

III.A.1. LOCATIONS & DATES

The study was conducted at 102 centers in the United States, Canada and Mexico. Patients were randomized in 96 of these centers. The first dose of single-blind medication was taken on 09 November 1998. The first and last doses of double-blind medication were taken on 10 December 1998 and 13 March 2000, respectively [clinstat\039.pdf:3].

III.A.2. SUMMARY

This was a Phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel-group study in patients with COPD, as defined by American Thoracic Society (ATS) guidelines. Patients had at least 11 visits over a 28-week period (Week –4, Screening, through Week 24). The study began with a 4-week, single-blind, placebo run-in period, after which eligible patients were randomized to receive either SB 207499 or matching placebo in a ratio of 2:1 for 24 weeks. One tablet of SB 207499 or matching placebo was taken twice daily, immediately after breakfast and after the evening meal. Albuterol MDI was used as rescue medication. This study was a duplicate of study 042 and 091 in all ways that reflected efficacy.

The primary efficacy endpoints were change from baseline in trough forced expiratory volume in one second ($FEV_{1.0}$) and change from baseline in total score of the St George's Respiratory Questionnaire (SGRQ). The primary comparison was the average difference between the SB 207499 treatment group and the placebo treatment group over the 24 weeks of the double-blind period.

Patients failing to complete the double-blind period were more frequent in the SB 207499 treatment group (31.8%) than in the placebo group (24.1%). This was largely due to premature discontinuations because of adverse events (SB 207499 21.8%, placebo 16.2%) that were not due to COPD exacerbations (SB 207499 20.2%, placebo 10.6%). Withdrawals from the SB 207499 group were mostly due to gastrointestinal complaints occurring during the double-blind treatment period (SB 207499 14.2%, placebo 2.3%). All percentages are based on the numbers of patients randomized to each treatment group. Compliance with the experimental treatment was 88.1% for patients assigned to

the SB 207499 group and was 97.2% for patients assigned to placebo. Concomitant medication were used to treat COPD exacerbations in 31.9% of placebo patients and in 18.3% of SB 207499 patients. Prednisone was used by 42% of patients in the placebo group and by 30.4% of the SB 207499 group who required concomitant medication to treat COPD exacerbations.

When averaged over 24 weeks of treatment and compared to baseline in a repeated measures analysis, there was a 10 mL increase in mean clinic trough $FEV_{1.0}$ in the SB 207499 group and a 30 mL decrease in the placebo group. Reduction from baseline in the trough $FEV_{1.0}$ of the placebo group that occurred over the first 4 weeks of treatment mostly drove the statistical significance of the primary efficacy endpoint. There was, though, a complementary but much smaller increase in the mean trough $FEV_{1.0}$ over the first 2 weeks of SB 207499 treatment. In the SB 207499 treatment group, the total score of the SGRQ decreased (improved) from baseline at Week 12, decreasing (improving) a bit more at week 24. The placebo group remained within 0.4 of baseline at both post-treatment visits, though the score did decrease (improve) from Week 12 to Week 24. Both primary endpoints were statistically significant after adjustment for multiple endpoints and the difference between treatment groups in changes from baseline of the total SGRQ achieved the minimum important difference. The improvement in the SGRQ was consistent and about equal over all three domains. Very minor changes in secondary and tertiary endpoints favored SB 207499 over placebo.

After the first dose of study medication, neither treatment group showed evidence of an acute effect over the subsequent four hours. No enhancement of albuterol-induced bronchodilation over the 30 minutes following the 4-hour post-first-dose spirogram was apparent in either treatment group. Over the first four hours following the last dose of study medication, the $FEV_{1.0}$ was unchanged in both treatment groups. After albuterol administration, the $FEV_{1.0}$ increased from the pre-treatment (4-hour post-last-dose) value by 150 mL in the placebo group and by 170 mL in the SB 207499 group. There was neither a first-dose effect nor a last-dose effect that differed between treatments. There was no enhancement of albuterol-induced bronchodilation four hours after the first dose, but there was slight improvement four hours after the last dose in the SB 207499 group compared with the placebo group.

III.A.3. OBJECTIVES

The objectives were to investigate the clinical efficacy of SB 207499 (15 mg twice daily) compared with placebo by the change in trough $FEV_{1.0}$ and total SGRQ score over 24 weeks in patients with COPD. The usual host of secondary efficacy and safety objectives were listed [clinstat\039.pdf:26].

III.A.4. DESIGN

This was a Phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel-group study in patients with COPD, as defined by American Thoracic Society (ATS) guidelines. Patients had at least 11 visits over a 28-week period (Week –4, Screening, through Week 24). Patients who did not enter the optional extension study had a safety follow-up visit 1 week after the last dose of study medication. The study began with a 4-week, single-blind, placebo run-in period, after which eligible patients were randomized to receive either SB 207499 or matching placebo in a ratio of 2:1 for 24 weeks. One tablet of SB 207499 or matching placebo was taken twice daily, immediately after breakfast and after the evening meal, in order to improve gastrointestinal tolerability.

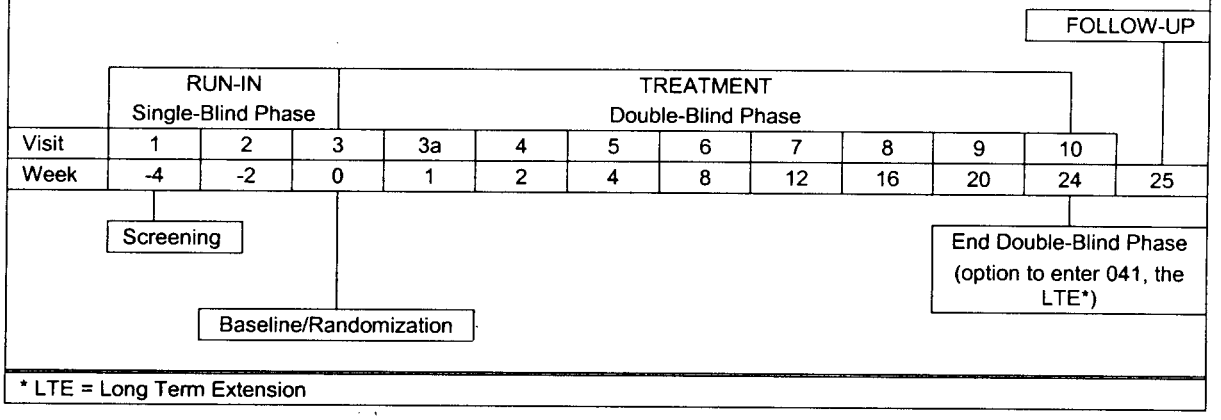
Pulmonary function tests (PFTs) were performed at all visits (with the exception of one safety-only visit at Week 1). At the screening visit (Week -4), pulmonary function (trough $FEV_{1.0}$, forced expiratory volume in 6 seconds {FEV6}, FVC, forced expiratory flow at 25-75% vital capacity {FEF_{25-75}}, forced expiratory flow at 75% vital capacity {FEF_{75}} and PEFR) were assessed before and after a standard dose of albuterol. At subsequent visits, pulmonary functions were measured in the absence of albuterol. In addition, the acute (first and last dose) effects of SB 207499 over a 4-hour time period, were explored at the beginning and at the end of the double-blind period (Weeks 0 and 24, respectively). At these two visits, the effects of albuterol on pulmonary function were assessed immediately after the 4-hour post-SB 207499 PFT determination. To ensure consistent and standardized data, centralized spirometry was employed at all centers.

Symptom-based assessments, such as exercise tolerance and breathlessness (modified Borg scale) were also performed at clinic visits. In addition, patients were asked to complete home diary cards recording COPD symptoms and albuterol use on a daily basis. The impact of COPD on patient quality of life was assessed using the SGRQ at baseline, Week 12 and Week 24 and the SF-36 (health survey questionnaire) at baseline and Week 24.

Safety assessments included adverse experiences, vital signs, ECGs, clinical laboratory tests, and, in a subset of patients, Holter monitoring. As a prompt for reporting adverse experiences at clinic visits, patients were asked to record in the diary if they feel differently since starting the study medication. In order to address concerns identified pre-clinically with SB 207499 and drugs of a similar pharmacological class for an effect on the gut vasculature and heart, the gastrointestinal adverse experience profile was defined and the ECG effects of SB 207499 were assessed. Particular attention was said to have been paid to collection of data on gastrointestinal adverse experiences with monitoring (physical exam, laboratory assessments, fecal occult blood, orthostatic heart rate and blood pressure) for events of potential concern. Gastrointestinal adverse experiences (i.e., bloody or black stool, abdominal discomfort such as pain or cramps, diarrhea, vomiting) which caused the patient concern or interfered with daily activities (including eating and sleeping) were to have been assessed by the Investigator within 24

hours of occurrence. The patient were to have been followed daily until resolution of these adverse experiences. In addition, Holter ECG monitoring was performed at particular centers on approximately 100 patients who participate in this study. Those patients who completed study 039 according to the protocol (i.e., through Week 24), had the option of entering the open-label long-term extension (LTE) study SB 207499/041. Patients who did not enter the long-term extension study or who withdrew before the end of Week 24 were asked to return for a safety follow-up visit 7 ± 3 days after the last dose of study medication [clinstat\039.pdf:27, 1978-9].

NDA #21573 (12/24/02, N-000) STUDY 039: SCHEMATIC REPRESENTATION OF STUDY DESIGN [clinstat\039.pdf:28, 1980]



III.A.5. PATIENTS

These included middle- and older-age COPD patients including both smokers and non-smokers. In order to obtain 450 evaluable patients, 645 patients were planned for randomization in a ratio of 2:1 for SB 207499 to placebo. Assuming a standard deviation of 12 units in the total score of the SGRQ, there was at least a 90% power to detect a 4-unit (empirically defined as the minimum clinically relevant difference) difference in the average of the 12- and 24-week assessments at a significance level of 0.025. For $FEV_{1.0}$, there was at least a 90% power to detect a difference of 120 mL assuming a standard deviation of 270 mL and the same significance level (0.025). Estimates of the standard deviation for both primary endpoints were obtained from previous Phase II studies of SB 207499 [clinstat\039.pdf:31-4,62, 1984-6].

III.A.5.a. INCLUSION CRITERIA

1. Male or female adults between 40 and 80 years of age, inclusive. Women of childbearing potential were required to have used effective contraceptive measures (i.e., oral contraceptives, Norplant, an IUD, a diaphragm with spermicide, a condom with spermicide or Depo-Provera) for at least 1 month prior to Visit 1 (Screening) and to continue using the same contraceptive measure during the study.

2. Patients with a clinical diagnosis of COPD, as defined by American Thoracic Society Guidelines [AMERICAN THORACIC SOCIETY. 1995. Standards for the Diagnosis and Care of Patients with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med,* 152, S77-S120. (ANI1307)].
3. Patients with a cigarette smoking history of ≥ 10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year or the equivalent). Both current smokers and ex-smokers were eligible.
4. Patients with a pre-albuterol $FEV_{1.0}$ to FVC ratio ($FEV_{1.0}$/FVC) ≤ 0.7 at Visit 1 (Screening).
5. Patients with fixed airway obstruction, defined by ≤ 15%, ≤ 200 mL, or both, increase in $FEV_{1.0}$ after the administration of albuterol 180 mcg via MDI with a spacer at Visit 1 (Screening).
6. Patients with a post-albuterol $FEV_{1.0}$ both ≥ 30% and ≤ 70% of predicted normal for height, age and sex at Visit 1 (Screening). Patients were assessed 15 to 30 (± 5) minutes after receiving albuterol 180 mcg via MDI with a spacer.
7. Patients who gave their signed written informed consent to participate.

III.A.5.b. EXCLUSION CRITERIA

1. Women who were pregnant or lactating.
2. Patients with asthma as the main component of their obstructive airways disease.
3. Patients with poorly controlled COPD, defined as the occurrence of any of the following in the 2 weeks prior to Visit 1 (Screening): acute worsening of COPD that was managed by the patient at home by self-treatment with corticosteroids or antibiotics, that required treatment prescribed by a physician, or for which the patient was hospitalized.
4. Patients with active tuberculosis, lung cancer, or clinically overt bronchiectasis.
5. Patients with clinically significant cardiovascular, neurological, renal, endocrine, or hematological abnormalities that were uncontrolled on permitted therapy.
6. Patients with clinically significant gastrointestinal or hepatic abnormalities.
7. Patients with a positive fecal occult blood test result between Visits 1 and 3 (Screening and Baseline).
8. Patients with clinically significant orthostatic changes in blood pressure or heart rate at Visit 1 (Screening) or 3 (Baseline).
9. Patients with a history of hypersensitivity to PDE4 inhibitors.
10. Patients with a history, or suspected history, of alcohol misuse or any other recreational substance abuse.
11. Patients who required treatment with inhaled cromolyn sodium or nedocromil, inhaled long-acting beta2-agonists, oral beta2-agonists, nebulized beta2-agonists, nebulized anticholinergics, xanthines, leukotriene modifiers or oral/inhaled corticosteroids beyond Visit 1 (Screening). All COPD medications except anticholinergic medication or albuterol via MDI were withdrawn prior to or at Visit 1 (Screening).

12. Patients receiving treatment with long-term oxygen therapy (LTOT), patients who required supplemental oxygen more often than on an occasional (prn) basis, or patients who required nocturnal positive pressure for sleep apnea.
13. Patients who had participated in a Pulmonary Rehabilitation Program within 4 weeks prior to Visit 1 (Screening) or who planned to enter a Pulmonary Rehabilitation Program during the study.
14. Patients who had received an investigational drug within 30 days of entry into this study, or within 5 drug half-lives of the investigational drug (whichever was longer).
15. Patients who had previously participated in an SB 207499 study and who received randomized study medication.
16. Patients unable to comply with study procedures (including completion of the quality of life questionnaires).

III.A.5.c. COMPLIANCE & RANDOMIZATION CRITERIA

Patients were randomized if the following four criteria were met in the placebo run-in period, assessed at Visit 3, Week 0 [clinstat\039.pdf:1996, 2029]:

1. Stability in Pulmonary Function: clinic trough $FEV_{1.0}$ (absolute value) in the absence of albuterol did not change (increased or decreased) by ≤ 20% between Visits 1 and 3.
2. Medication Compliance: patients must demonstrate ≥ 80% and ≤ 120% compliance since the previous visit in taking single-blind study medication.
3. Diary Compliance: complete diary card data on at least 20 days during the 28-day placebo run-in period.
4. Diary Symptom Score: a total symptom score (cough + sputum production + breathlessness) of 3 or more on at least 5 of the 10 days immediately prior to this visit. Each of the components was rated on a 0-4 (breathlessness) or 0-3 scale (cough, sputum production).

III.A.6. TREATMENT

SB 207499 was provided as off white, round, convex tablets containing 15 mg of SB 207499. Placebo tablets, identical in appearance to the active medication, were provided for the single-blind placebo run-in phase and for the placebo arm of the double-blind phase of the study. The appearance, formulation, and batch numbers of the study medication are in the following table:

NDA #21573 (12/24/02, N-000) STUDY 039: APPEARANCE, FORMULATION AND BATCH NUMBERS OF STUDY MEDICATION [clinstat\039.pdf:34]√

Study Drug	Appearance	Formulation	Dose	Batch Number
SB 207499	off-white, round, convex	tablet	15 mg	U97093
placebo	off-white, round, convex	tablet	--	U98008

Appendix A contains the Certificate of Analysis [clinstat\039.pdf:1949].

For the single-blind placebo run-in phase, SB 207499-matched placebo tablets were supplied in bottles containing 34 tablets. For the double-blind treatment phase, bottles contained either 34 tablets of SB 207499 15 mg or matching placebo. Each bottle provided a 17-day supply of study medication to allow for some flexibility in the interval between visits. For visits where two bottles were dispensed, dosing instructions included a statement indicating that the patient should finish all tablets in one bottle before opening the next.

During the run-in phase, patients took one SB 207499-matched placebo tablet twice daily, in the morning immediately after breakfast and in the evening immediately after a meal. Patients who fulfilled the randomization criteria entered a 24-week double-blind treatment phase. One tablet of study medication was taken twice daily, in the morning immediately after breakfast and in the evening immediately after a meal. Throughout the study, patients did not take the morning dose of study medication before attending morning clinic visits. If an afternoon visit was scheduled, patients were instructed to take the morning dose of study medication after breakfast, which was at least 8 hours before their clinic visit. On the day of clinic visits, the first dose of study medication was administered in the clinic with food after completion of efficacy and safety assessments [clinstat\039.pdf:34-5].

III.A.6.a. RESCUE MEDICATION

The use of albuterol 90 mcg/actuation, 200 actuations per canister (MDI with or without a spacer) on an "as-needed" (prn) basis was permitted throughout the study and recorded every evening in the diary card. If the patient experienced symptoms which did not respond adequately to rescue medication (e.g., albuterol, 2 actuations every 4 hours), the patient was to contact the Investigator. If a patient occasionally used albuterol at an interval of less than every 4 hours (did not exceed twice a day at the reduced interval, i.e., 16 puffs/day), the patient remained in the trial at the discretion of the Investigator [clinstat\039.pdf:36].

III.A.6.b. COMPLIANCE

Compliance was assessed by counting the number of remaining pills at all study visits. Patients were required to show 80-120% compliance in taking study medication at each visit (with the exception of Week -2) to continue in the study [clinstat\039.pdf:36].

III.A.6.c. PRIOR, CONCOMITANT & PROHIBITED MEDICATIONS

All medications for COPD, including inhalers, taken during the 3 months preceding the Screening Visit were recorded, together with all other medications taken within 2 weeks of the visit. Prohibited respiratory medications were discontinued prior to or at the Screening Visit. Combination therapies (beta2-agonist anticholinergic mix)

were changed to separate single therapy inhalers with equivalent doses, prior to, or at, Screening.

All concomitant medications taken during the study were recorded in the CRF with the indication, unit dose, frequency and dates of administration. In addition to albuterol, provided as rescue medication, stable doses of anticholinergic medication by MDI and mucolytics were also permitted during the study. Patients using mucolytics prior to study start continued to do so at a stable dose, but mucolytic administration was not begun during the study.

The following medications were prohibited throughout the study except for the short-term (< 2 weeks) management of COPD exacerbations:

corticosteroids (inhaled or oral)
xanthines
inhaled cromolyn sodium or nedocromil
inhaled long-acting beta2-agonists
inhaled short-acting beta2-agonists other than albuterol
oral or nebulized beta2-agonists
nebulized anticholinergics
leukotriene modifiers

If clinically indicated, inhaled/oral steroids or antibiotics were permitted for a short course (< 14 days) for the treatment of an exacerbation of COPD. COPD exacerbations were categorized as Level 1, 2, or 3, based on the treatment received by the patient for the exacerbation. Patients who experienced more than three Level 2 or Level 3 exacerbations during the double-blind treatment period were to have been withdrawn. Patients who took any corticosteroids or antibiotics for the treatment of a COPD exacerbation during the run-in phase were not to have been randomized.

NDA #21573 (12/24/02, N-000) STUDY 039: COPD EXACERBATION CATEGORIES [clinstat\039.pdf:2044]√	
Level	**Description**
1	Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).
2	Acute worsening of COPD that requires additional treatment (e.g., a short course of oral steroids, antibiotics, etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).
3	Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

All medications prescribed for the treatment of COPD exacerbations were recorded in a separate section of the CRF. Combinations of inhaled beta2-agonist and anticholinergic drugs were not permitted during the study, but changed to separate, single-therapy inhalers prior to, or at, Screening. Theophylline was not permitted at any time during the study [clinstat\039.pdf:36-7, 1981].

III.A.7. VARIABLES

The primary efficacy endpoints were change from baseline in pre-albuterol trough forced expiratory volume in one second ($FEV_{1.0}$) and change from baseline in total score of the St George's Respiratory Questionnaire (SGRQ). The primary comparison was the average difference between the SB 207499 treatment group and the placebo treatment group over the 24 weeks of the double-blind period. The modified intent-to-treat population was to have included all patients who received randomized study medication, had a baseline efficacy evaluation and at least one on-therapy efficacy evaluation during the double blind period. The modified intent-to-treat population is the primary population in this study [clinstat\039.pdf:47, 2052, 2054-5].

Secondary efficacy variables included: post-exercise breathlessness (modified Borg scale); summary symptom score (comprising the sum of scores for cough, sputum and breathlessness recorded on domiciliary diary card); clinic FVC at trough; exercise performance (distance walked during 6-minute walk); and, COPD exacerbation rate. The exacerbation-free survival rate at 24 weeks and associated 95% confidence intervals was estimated for each treatment group using the Kaplan-Meier product limit.

Fifteen tertiary efficacy variables were also defined: use of 'as needed' albuterol; clinic PEFR at trough; first and last dose effect on pulmonary function tests (clinic $FEV_{1.0}$, clinic, PEFR, clinic FVC, clinic FEF_{25-75}, clinic FEF_{75}, and clinic FEV6); overall breathlessness during usual activity (modified Borg scale); subscales of SF-36 (generic quality of life); health economic endpoints (days off work, healthcare utilization); subscales of SGRQ (disease specific quality of life) including symptoms, impacts and activities; clinic FEF_{25-75} at trough; individual components of summary symptom score (cough, sputum production, breathlessness); post exercise SaO_2; SaO_2 at rest in patients with $FEV_{1.0}$ of < 40% predicted for age, height and gender; arterial blood gases (PaO_2 and $PaCO_2$) in patients with $FEV_{1.0}$ of < 40% predicted for age, height and gender; symptom-free days; clinic FEF_{75} at trough; and, clinic FEV6 at trough [clinstat\039.pdf:47-8, 2052-7].

Evaluation of safety data included all randomized patients and was based on comparisons of patient experience by assigned medication regimen. Clinical interpretation was based on review of displays of adverse experiences. Principal considerations in this evaluation were time-to-onset, severity, study medication and Investigator-reported relationship of the adverse experience to study medication. Descriptive statistics were also used in the evaluation of safety. If the sample size was adequate, exploratory analyses may also have been performed to characterize the specified gastrointestinal adverse experiences [clinstat\039.pdf:2057].

When overt or occult blood was found in the stool, neither referral to a Gastroenterologist nor colonoscopy to investigate the cause were mandated in this protocol but were left to the discretion of the investigator [clinstat\039.pdf:2126-30].

Patients were required to have refrained from using albuterol or anticholinergic medication or smoking during the 2-hour period preceding each visit. For each scheduled study visit, patients were required to attend the clinic in the morning, at the same time and after breakfast. Clinic visits were scheduled at 10:00 a.m. ± 2 hours. Avoidance of smoking and the use of albuterol or anticholinergic treatments during the clinic stay was attempted, if at all possible. Patients were not to take their morning doses of study medication before attending morning clinic visits [clinstat\039.pdf:1988].

Pulmonary function tests (PFTs) were performed at all visits (with the exception of one safety-only visit at Week 1). At the screening visit (Week -4), the following pulmonary functions were evaluated before and after a standard dose of albuterol:

trough forced expiratory volume in one second ($FEV_{1.0}$)
forced expiratory volume in 6 seconds (FEV6)
forced vital capacity (FVC)
forced expiratory flow at 25-75% vital capacity (FEF_{25-75})
forced expiratory flow at 75% vital capacity (FEF_{75})
peak expiratory flow rate (PEFR)

At subsequent visits, pulmonary function were measured in the absence of albuterol. In addition, the acute (first and last dose) effects of SB 207499 over a 4-hour time period, were explored with serial pulmonary function tests at the beginning and at the end of the double-blind period (Weeks 0 and 24, respectively). At these two visits, the effects of albuterol on pulmonary function were assessed immediately after the 4-hour post SB 207499 assessment. At that time 360 mcg of albuterol was administered through a spacer device and another pulmonary function evaluation was performed 30 minutes thereafter. To ensure consistent and standardized data, centralized spirometry were employed at all centers [clinstat\039.pdf:1978, 1997-8, 2016-7].

Symptom-based assessments, such as exercise tolerance and breathlessness (modified Borg scale, 0-10 scale assessed both reflectively and instantaneously after six minutes of exercise) were performed at clinic visits. The reflective question was:

"Generally speaking, how short of breath have you been during the previous week when you carried out tasks that usually cause you to be short of breath (e.g., walking, carrying shopping, climbing stairs, etc.)?"

...and the instantaneous question asked immediately after a six-minute exercise test was:

"How short of breath do you feel right now?"

The modified Borg breathlessness scale used a scoring system half of which is devoted to subtle distinctions in the most serious subjective impairment, as shown below [clinstat\038,pdf:2021-2]:

NDA #21573 (12/24/02, N-000) STUDY 039: MODIFIED BORG BREATHLESSNESS SCALE [clinstat\039.pdf:2021-2]√	
0	nothing at all
1	very, very slight (just noticeable)
2	very slight
3	moderate
4	somewhat severe
5	severe
6	
7	very severe
8	
9	very, very severe (almost maximal)
10	maximal

In addition, patients were asked to complete home diary cards recording COPD symptoms and albuterol use on a daily basis. The COPD symptoms include breathlessness, cough and sputum production and were each rated, breathlessness on a 5-point scale, and cough and sputum production on 4-point scales. The summary score was an 11-point scale of 0 to 10 according to the following criteria [clinstat\039.pdf:2029, 2/26/03 response to FDA questions 1/30/03]:

NDA #21573 (12/24/02, N-000) STUDY 039: DIARY COPD SYMPTOM SCORES [clinstat\039.pdf:2029, 2/26/03 response to FDA questions 1/30/03]√			
	BREATHLESSNESS	**COUGH**	**SPUTUM PRODUCTION**
0	not breathless at rest or on exertion	no cough	none
1	not breathless at rest, but breathless on moderate exertion (e.g. walking quickly)	mild cough (i.e. some, mostly morning)	small amount of sputum
2	not breathless at rest, but breathless on mild exertion (e.g. walking on level ground)	moderate cough (i.e. some morning and evening)	moderate amount of sputum
3	not breathless at rest, but breathless on minimal exertion (e.g. getting washed)	severe cough	large amount of sputum
4	breathless at rest	n/a	n/a

The impact of COPD on patient quality of life was assessed using the St. George's Respiratory Questionnaire (SGRQ) at baseline, Week 12 and Week 24 and the SF-36 (health survey questionnaire) at baseline and Week 24 [clinstat\039.pdf:1968, 1978, 2094-108].

Safety assessments included adverse experiences, vital signs, ECGs, clinical laboratory tests, and, in a subset of 100 patients, Holter monitoring. As a prompt for reporting adverse experiences at clinic visits, patients were asked to record in the diary if they felt differently since starting the study medication. Gastrointestinal adverse experiences (i.e., bloody or black stool, abdominal discomfort such as pain or cramps, diarrhea, vomiting) which caused the patient concern or interfere with daily activities (including eating and sleeping) were to have been assessed by the Investigator within 24 hours of occurrence. The patient was to have been followed daily until resolution of these adverse experiences [clinstat\039.pdf:1968].

Blood samples for pharmacokinetic analysis of SB 207499 and the metabolite SB-217493 plasma concentration data were collected from all patients randomized into the study. Patients were be required to provide six samples during the 24-week period of double-blind treatment. At Visit 3 (Week 0) one sample was drawn 3 hours post-dose. At Visit 5 (Week 4), pre-dose and post-dose (either between 0.5 and 2 hours or between 1.5 and 3 hours) samples were drawn. At Visit 7 (Week 12), pre-dose and post-dose (either between 3 and 6 hours or between 5 and 10 hours) blood samples were to be drawn. At Visit 10 (Week 24), a pre-dose blood sample was to be drawn. A sample was also collected from patients reporting to the clinic for an unscheduled visit triggered by a gastrointestinal adverse experience (or a serious adverse experience whenever practicable), to compliment the PK/PD analysis [clinstat\039.pdf:1970].

At Visit 1 or at the patient's next visit which included scheduled blood collection (Visits 3 through 7, 10), a 7 ml whole blood sample for DNA extraction was to be requested from every patient. The DNA was to be used to determine if there was association of any particular genes with COPD or the clinical features of the disease. Examples of genes that may have been studied are: PDE IV, epoxide hydrolase, 5-LO, seven transmembrane receptors, alpha-1 antitrypsin. Participation in the DNA sampling studies was optional [clinstat\039.pdf:1971].

Those patients who completed study 039 according to the protocol (i.e., through Week 24), had the option of entering the open-label long-term extension (LTE) study SB 207499/041. Patients who did not enter the long-term extension study or who withdrew before the end of Week 24 were asked to return for a safety follow-up visit 7 ± 3 days after the last dose of study medication [clinstat\039.pdf:1968, 1979].

III.A.8. PROCEDURE FLOW CHART

NDA #21573 (12/24/02, N-000) STUDY 039: PROCEDURE FLOW CHART [CLINSTAT\039.PDF:1982-3]													
	Screen		Base-line								End DB	Early W/D[1]	Safety F/U[2]
Visit	1	2	3	3a	4	5	6	7	8	9	10		
Week	-4	-2	0	+1	+2	+4	+8	+12	+16	+20	+24		+25
medical & surgical history	X												
PA chest radiograph[3]	X												
DLCO[4]	X												
pulmonary history & symptoms	X												
medication history	X												
St. George's Respiratory Questionnaire (SGRQ)			X					X			X	X	
SF-36			X								X	X	
study medication compliance		X	X	X	X	X	X	X	X	X	X	X	
concomitant medications/procedures		X	X	X	X	X	X	X	X	X	X	X	X
baseline signs, symptoms & adverse events		X	X	X	X	X	X	X	X	X	X	X	X
exacerbation assessment/resource use	X	X	X	X	X	X	X	X	X	X	X	X	X
overall breathlessness (modified Borg Scale)	X	X	X		X	X	X	X	X	X	X		
diary card review		X	X	X	X	X	X	X	X	X	X	X	
physical examination (PE)[5]	X		X								X	X	X[6]
vital signs (BP, HR)	X[7]	X	X[7]	X	X	X	X	X	X	X	X[7]	X[7]	X
resting 12-lead electrocardiogram (ECG)	X		X	X	X	X	X	X	X	X	X	X	X[6]
Holter monitoring[8]		X		X						X			
exercise tolerance (6-minute walk)	X	X	X			X	X	X	X	X	X		
post-exercise SaO_2 & breathlessness	X	X	X			X	X	X	X	X	X		
albuterol reversibility [9]	X												
pulmonary functions (PFTs) without albuterol[10]		X	X		X	X	X	X	X	X	X	X	X
hourly PFTs for 4 hours post first & last dose[11]			X								X		
laboratory tests	X[18]		X[12]	X	X	X	X	X	X[13]	X[13]	X[12]	X[12]	X[6, 13]
pharmacokinetic evaluations (PK)[14]			X			X		X			X		
arterial blood gas (ABG) & SaO_2 [15]			X								X		

1. Patients who stop taking study medication between clinic visits will attend the clinic within 24 hours for an early withdrawal visit.
2. Patients who enter the open-label extension study do not require a final safety follow-up visit.
3. Postero-anterior chest X-ray must be performed at Visit 1 unless the film from a chest X-ray within the 12 weeks prior to Visit 1 is available to the Investigator.
4. DLCO should be done between Visit 1 and Visit 3 if not performed during the previous 24 weeks or if the results are unavailable.

5. To include a respiratory examination.
6. If abnormalities at previous visit for patients who complete Visit 10 and do not enter the extension study (041) or withdraw from the study.
7. Including Orthostatic vital signs.
8. In 100 patients at selected sites. Holter monitoring for 48 hours at Visit 2 and for 24 hours at Visits 3a and 9.
9. Before and 15 to 30 (5) minutes after administration of 180 mcg albuterol via a MDI with a spacer to determine % predicted $FEV_{1.0}$, FEV6, FVC, FEF_{25-75}, FEF_{75}, PEFR, and $FEV_{1.0}$/FVC.
10. Includes $FEV_{1.0}$, FEV6, FVC, FEF_{25-75}, FEF_{75}, PEFR, and $FEV_{1.0}$/FVC measured by centralized spirometry by the same person at each visit.
11. Pulmonary function tests 30 (±5) minutes after albuterol following the 4-hour post-dose assessment at Visits 3 and 10.
12. In addition to usual laboratory tests, three fecal occult blood tests will be performed between Visits 1 and 3, between Visits 9 and 10, and at early withdrawal; amylase will be measured at Visit 3.
13. Urinary beta-HCG tests will be performed in females of childbearing potential. No other laboratory samples will be collected at Visits 8 and 9.
14. Visit 3: 3 hours post-dose. Visit 5: trough and 0.5-3 hours post-dose. Visit 7: trough and 3-10 hours post-dose. Visit 10: trough only.
15. In patients with < 40% of predicted $FEV_{1.0}$ at Visit 1 only.
16. Redispense medication dispensed at Visit 3.
17. If a patient enters the long-term extension study, this record will be completed at Visit 10.
18. Includes blood that will be collected for DNA extraction (procedure is optional). If patient has completed screening prior to Amendment 1, blood may be collected at patient's next visit which includes a blood draw for hematology and clinical chemistry (Visits 3 through 7, 10).

III.A.9. STATISTICS

The modified intent-to-treat population was to have included all patients who received randomized study medication, had a baseline efficacy evaluation and at least one on-therapy efficacy evaluation during the double blind period. The modified intent-to-treat population was the primary efficacy population in this study [clinstat\039.pdf:2052, 2054-5].

In all statistical models used in the efficacy analysis, where the effect of center was present, centers enrolling less than six patients were combined. The assessment of treatment differences for the primary efficacy variables was based on a repeated measures model with effects for treatment, center and time. Age, gender and smoking status may also have been included in the model as covariates. Several correlation structures were explored including compound symmetry, unstructured and spatial correlation.

Prior to testing for the average treatment effect over 24 weeks, a full model was examined to test for the effects of age, gender, smoking status, treatment-by-center interaction, treatment by-time interaction and time-by-center interaction. The effects of age, gender and smoking status were removed if they were found, to be non-significant. Each interaction effect was tested at a significance level of 0.10. If evidence of a treatment-by-center interaction was found, exploratory analyses were undertaken to describe the nature of the interaction and results presented by center.

The durability of treatment effect was further assessed using repeated measures models. If no evidence of interactions was observed, the test for the average treatment effect over 24 weeks was based on a reduced model with all interaction effects removed. Least squares means along with associated 95% confidence intervals were calculated for each treatment group. Least squares means and ninety-five percent (95%) confidence intervals were also calculated for the treatment difference.

Differences between treatment groups were assessed using T-tests on the least square means. To control the overall Type I error, the significance level in the test for treatment differences in the primary endpoints were adjusted using the modified Bonferroni procedure of Hochberg [clinstat\039.pdf:62, 2055-6].

III.A.10. DISPOSITION

The message to be drawn from the table below is that there were a lot of dropouts which introduced many missing data points and were more frequent in the SB 207499 treatment group [clinstat\039.pdf:73].

NDA #21573 (12/24/02, N-000) STUDY 039: PATIENT DISPOSITION [clinstat\039.pdf:73, 250-1, 267]√			
	Treatment Group		
Disposition	Placebo n (% of randomized)	SB 207499 (15 mg bid) n (%of randomized)	Total n (%of randomized)
entered single-blind phase	--	--	937
randomized	216 (100)	431 (100)	647 (100)
withdrawn from double-blind phase	52 (24.1)	137 (31.8)	189 (29.2)
modified ITT efficacy analysis	207 (95.8)	378 (87.7)	585 (90.4)
PP efficacy analysis	188 (87.0)	339 (78.7)	527 (81.5)
safety analysis	216 (100)	431 (100)	647 (100)
completed double-blind phase	164 (75.9)	294 (68.2)	458 (70.8)
entered open-label extension (LTE)	140 (64.8)	214 (49.7)	354 (54.7)

Patients failing to complete the double-blind period were more frequent in the SB 207499 treatment group (31.8%) than in the placebo group (24.1%). This is a somewhat unusual finding for a treatment that is supposed to make patients feel better. In attempting to understand the reason for the large number of dropouts, the sponsor introduced the table that follows:

NDA #21573 (12/24/02, N-000) STUDY 039: REASON FOR EARLY TERMINATION BY TREATMENT GROUP [clinstat\039.pdf:75,267]√		
	Treatment	
Withdrawal Reason	Placebo (n = 216) n (%)	SB 207499 (n = 431) n (%)
adverse events	35 (16.2)	94 (21.8)
COPD exacerbation	12 (5.6)	7 (1.6)
not due to a COPD exacerbation	23 (10.6)	87 (20.2)
insufficient therapeutic effect	4 (1.9)	7 (1.6)
protocol deviation, including non-compliance	2 (0.9)	8 (1.9)
lost to follow-up	6 (2.8)	8 (1.9)
other	5 (2.3)	20 (4.6)
total withdrawn prematurely	52 (24.1)	137 (31.8)
completed double-blind phase	164 (75.9)	294 (68.2)

The most frequent reason for early termination in both treatment groups was "adverse events" which were about 1/3 more frequent in the SB 207499 group than in the placebo group. Apparently, this was the primary contributor to the overall disparity in early terminators between the two treatments. Premature discontinuations because of adverse events attributable to something other than "COPD exacerbation" were twice as frequent in the SB 207499 group than in the placebo group. This raises the obvious question, what adverse events were the source of this disparity?

Thirty-five of 216 (16.2%) placebo patients and 94 of 431 (21.8%) patients in the SB 207499 group were withdrawn from double-blind treatment due to an adverse event. A very large portion of the SB 207499 group discontinued prematurely due to gastrointestinal complaints (14.2%) occurring during the double-blind period, compared with placebo (2.3%). There was a higher incidence of COPD exacerbations in the placebo group leading to withdrawal than in the SB 207499 group (5.6% and 1.6%,

respectively) [clinstat\039.pdf:156-7, 159-65]. All of these percentages are based on the number of randomized patients.

III.A.11. DEMOGRAPHICS

This was almost exclusively a trial conducted in Caucasians. Males were the most frequent gender in both treatment groups. The dominant age range of patients enrolled in this COPD study was over 50, with a mean of 65 years. By inspection, the medians are very close to the means which suggests a fairly symmetrical distribution without much skewness. The frequencies of most characteristics were fairly evenly distributed between treatment groups. The exceptions were: the $FEV_{1.0}$ (L) which was 110 mL greater in the placebo group than in the SB 207499 group; the Black race, which was three times more frequent in the treatment group than in the placebo group; the female gender, which was 1/3 more frequent in the treatment group; and, the use of inhaled corticosteroids during the three months before study entry, which was 1/3 more frequent in the placebo group. Other baseline demographic characteristics of interest are shown in the following table [clinstat\039.pdf:81, 84, 275, 280].

NDA #21573 (12/24/02, N-000) STUDY 039: DEMOGRAPHIC CHARACTERISTICS AT SCREENING (ALL RANDOMIZED PATIENTS) [clinstat\039.pdf:81, 84, 275, 280]√

		Treatment Group			
		Placebo n = 216		SB 207499 15 mg bid n = 431	
Characteristic		n	(%)	n	(%)
Sex	Female	70	(32.4)	178	(41.3)
	Male	146	(67.6)	253	(58.7)
Race	Caucasian	209	(96.8)	394	(91.4)
	Hispanic	2	(0.9)	9	(2.1)
	Black	3	(1.4)	19	(4.4)
	Asian	0	(0.0)	1	(0.2)
	Oriental	0	(0.0)	3	(0.7)
	Other*	2	(0.9)	5	(1.2)
Age, years	< 50	12	(5.6)	15	(3.5)
	50 - 65	96	(44.4)	188	(43.6)
	> 65	108	(50.0)	228	(52.9)
	Mean (SD)	64.9 (8.4)		65.4 (8.6)	
	Median	65.5		66.0	
	Min, Max	41, 80		41, 82	
Weight, kg.	Mean (SD)	78.6 (17.7)		77.5 (17.9)	
	Min, Max	37, 140		39, 141	
Corticosteroid Use**	Inhaled	70	(32.4)	107	(24.8)
	Oral	2	(0.9)	8	(1.9)
$FEV_{1.0}$ (L)	MEAN (SD)	1.48 (0.55)		1.37 (0.49)	
	Min, Max	0.53, 3.24		0.47, 2.92	
Reversibility (%)	MEAN (SD)	6.7 (7.6)		7.7 (7.1)	

NDA #21573 (12/24/02, N-000) STUDY 039: DEMOGRAPHIC CHARACTERISTICS AT SCREENING (ALL RANDOMIZED PATIENTS) [clinstat\039.pdf:81, 84, 275, 280]√					
		Treatment Group			
		Placebo n = 216		SB 207499 15 mg bid n = 431	
Characteristic		n	(%)	n	(%)
	MIN, MAX	-32.5, 30.2		-8.5, 34.0	
* not further defined	** number of patients who used oral and inhaled corticosteroids				

III.A.12. COMPLIANCE WITH TREATMENT

Patients were to be withdrawn from the study if study medication compliance was not ≥ 80% and ≤ 120%. The following table shows that a greater percentage of placebo patients were compliant with their treatment than were SB 207499 treated patients [1/31/03 clinstat\039.pdf:93].

NDA #21573 (12/24/02, N-000) STUDY 039: STUDY MEDICATION COMPLIANCE BY PATIENTS [1/13/03 clinstat\039.pdf:93]√		
Compliance (%)	Treatment Group	
	Placebo (N = 213) n (%)	SB 207499 15 mg BID (N = 427) n (%)
< 80	6 (2.8)	51 (11.9)
80 - 120	207 (97.2)	376 (88.1)
> 120	0	0
mean (SD)	96.59 (7.16)	92.19 (15.05)
Min, Max	44.12, 107.95	5.26, 116.67

III.A.13. CONCOMITANT COPD MEDICATION USE

The numbers (%) of patients with COPD exacerbations requiring treatment during the double-blind treatment period are shown below. A total of 32% of placebo patients and 18% of patients treated with SB 207499 required concomitant medication for an exacerbation of their underlying disease. Individual medications taken by at least 2% of patients for a COPD exacerbation are listed. Prednisone was used by 42% of patients in the placebo group and by 30.4% of the SB 207499 group who required concomitant medication to treat COPD exacerbations. These data are presented in the following table [1/31/03 clinstat\039.pdf:92].

NDA #21573 (12/24/02, N-000) STUDY 039: NUMBERS OF PATIENTS (%) USING CONCOMITANT MEDICATIONS TO TREAT COPD EXACERBATIONS [1/13/03 clinstat\039.pdf:92]√		
COPD Medication	Treatment Group	
	Placebo (N = 216) n (%)	SB 207499 15 mg BID (N = 431) n (%)
TOTAL*	69 (31.9)	79 (18.3)
prednisone	29 (13.4)	24 (5.6)
salbutamol	15 (6.9)	18 (4.2)
azithromycin	10 (4.6)	10 (2.3)
ipratropium bromide	8 (3.7)	10 (2.3)
guafenesin	12 (5.6)	9 (2.1)

NDA #21573 (12/24/02, N-000) STUDY 039: NUMBERS OF PATIENTS (%) USING CONCOMITANT MEDICATIONS TO TREAT COPD EXACERBATIONS [1/13/03 clinstat\039.pdf:92]√		
COPD Medication	Treatment Group	
	Placebo (N = 216) n (%)	SB 207499 15 mg BID (N = 431) n (%)
levofloxacin	6 (2.8)	9 (2.1)
clarithromycin	9 (4.2)	7 (1.6)
fluticasone propionate	5 (2.3)	6 (1.4)
amoxacillin trihydrate	6 (2.8)	3 (0.7)
* Total represents total number of patients receiving medication for COPD exacerbations.		

III.A.14. EFFICACY

III.A.14.a. PRIMARY MEASURES

All efficacy measures were analyzed in the modified intent-to-treat population, defined as all patients who received randomized study medication and had a baseline evaluation and at least one on-therapy efficacy evaluation during the double-blind period. The change from baseline in trough $FEV_{1.0}$ averaged over 24 weeks of treatment (Weeks 2, 4, 8, 12, 16, 20 and 24) is presented in the next table.

NDA #21573 (12/24/02, N-000) STUDY 039: SUMMARY OF DIFFERENCE BETWEEN TREATMENTS IN AVERAGE CHANGE FROM BASELINE OVER 24 WEEKS (REPEATED MEASURES ANALYSIS) IN TROUGH $FEV_{1.0}$ (L) – ITT GROUP [clinstat\039.pdf:95, 401]√									
Treatment Group	N	Change From Baseline				Comparison With Placebo			
		Mean*	SEM	Lower 95% CI	Upper 95% CI	Mean Diff.	Lower 95% CI	Upper 95% CI	Type I Error**
placebo	207	-0.03	0.01	-0.05	-0.01	--	--	--	--
SB 207499	378	0.01	0.01	-0.01	0.03	0.04	0.01	0.06	0.002
* Mean values are adjusted for center and week.									
** This was corrected for multiple comparisons by the modified Bonferroni procedure of Hochberg.									

The numbers of patient in the two treatment groups were fewer than the number who were randomized (placebo = 216, SB 207499 = 431). This means that either these patients failed to provide a baseline spirometry or dropped out before the first post-treatment spirometry was determined [7/9/03 Teleconference, 03-07-09_Tel.pdf].

When averaged over 24 weeks of treatment and compared to baseline, there was a 10 mL increase in mean clinic trough $FEV_{1.0}$ in the SB 207499 group and a 30 mL decrease in the placebo group. There was a statistically significant ($p \leq 0.002$) difference between the two treatment groups in mean trough change in $FEV_{1.0}$ of 40 mL. Analyses of the $FEV_{1.0}$ of patients who completed the study and patients who withdrew from the study, with missing values in the latter group imputed with the worst $FEV_{1.0}$, were similar. This was cited as evidence of similarity between completers and those who withdrew [clinstat\039.pdf:94-5, 99, 401, 01/31/03 clinstat\039.pdf:3857, 3865].

The baseline difference in $FEV_{1.0}$ between the two treatment groups was 100 mL which indicates that randomization had not evenly distributed this measure between the two treatment groups. Neither this small disparity nor the possible causes of it were addressed in this study report. Reduction from baseline in the trough $FEV_{1.0}$ of the placebo group (about 50 mL) that occurred over the first 4 weeks of treatment mostly drove the statistical significance of the primary efficacy endpoint. Though, there was a complementary small increase in the mean trough $FEV_{1.0}$ over the first 2 weeks of SB 207499 treatment of about 30 mL. The mean trough $FEV_{1.0}$ at each visit for each treatment group is shown in the next table:

NDA #21573 (12/24/02, N-000) STUDY 039: MEAN TROUGH $FEV_{1.0}$ (L) IN THE ITT POPULATION BY VISIT AND TREATMENT GROUP [clinstat\039.pdf:97, 402]√

Week	SB 207499		Placebo	
	N (% Baseline)	Mean* (SEM)	N (% Baseline)	Mean* (SEM)
Baseline	394	1.33 (0.03)	208	1.43 (0.04)
2	377	1.36 (0.03)	206	1.40 (0.04)
4	358	1.34 (0.03)	195	1.38 (0.04)
8	333	1.34 (0.03)	190	1.37 (0.04)
12	314	1.35 (0.04)	183	1.37 (0.04)
16	308	1.36 (0.04)	179	1.38 (0.04)
20	297	1.37 (0.04)	170	1.39 (0.05)
24	294	1.36 (0.04)	164	1.38 (0.05)
Endpoint	394	1.34 (0.03)	208	1.36 (0.04)

* mean values were adjusted for center

Both groups showed a reduction in patient numbers at successive visits, presumably because of dropouts. The percent declines in patient numbers from baseline to Week 24 were 25.4% in the SB207499 group and 21.2% in the placebo group.

The SGRQ has a 101 point scale size (lower scores represent greater wellness), is divided into three domains and a minimum important difference of four units [www.atsqol.org most recent update April 2002]. The average change from baseline in total score of the SGRQ over 24 weeks of treatment is presented in the table that follows. This average was derived from testing done at baseline, Week 12 and Week 24.

NDA #21573 (12/24/02, N-000) STUDY 039: SUMMARY OF DIFFERENCE BETWEEN TREATMENTS IN AVERAGE CHANGE FROM BASELINE OVER 24 WEEKS (REPEATED MEASURES ANALYSIS) IN SGRQ TOTAL SCORE – ITT GROUP [clinstat\039.pdf:99, 421]√

Treatment Group	N	Change From Baseline				Comparison With Placebo			
		Mean*	SEM	Lower 95% CI	Upper 95% CI	Mean Diff.	Lower 95% CI	Upper 95% CI	Type I Error
placebo	181	0.4	0.8	-1.3	2.0	--	--	--	--
SB 207499	310	-3.7	0.7	-5.1	-2.4	-4.1	-6.0	-2.2	0.000

* Mean values were adjusted for center and week.

As before, the numbers of patient in the two treatment groups were fewer than the numbers who were randomized. This means that either these patients failed to

provide a baseline SGRQ or dropped out before the first post-treatment SGRQ was determined [7/9/03 Teleconference, 03-07-09_Tel.pdf].

In the SB 207499 treatment group, the total score of the SGRQ decreased (improved) from baseline at Week 12, decreasing a bit more at week 24. The placebo group remained within 0.4 of baseline at both post-treatment visits, though the score did decrease (improve) from Week 12 to Week 24.

NDA #21573 (12/24/02, N-000) STUDY 039: MEAN SGRQ (TOTAL SCORE) IN THE ITT POPULATION BY VISIT AND TREATMENT GROUP [clinstat\039.pdf:101, 422]√

Week	SB 207499		Placebo	
	N	Mean* (SEM)	N	Mean* (SEM)
Baseline	340	45.0 (0.9)	196	44.6 (1.2)
12	306	41.4 (1.1)	181	44.8 (1.4)
24	286	40.4 (1.2)	161	44.5 (1.5)
Endpoint	340	41.1 (1.0)	196	45.4 (1.3)

* mean values were adjusted for center

Analyses of the SGRQ Total Score of patients who completed the study and patients who withdrew from the study, with missing values in the latter group imputed with the worst SGRQ, were similar in mean changes from baseline of the SB 207499 groups (completers -4.1, withdrawals with worst score imputation -3.7). This was cited as evidence of similarity between completers and those who withdrew. Placebo patients who completed the study had a mean change from baseline in SGRQ Total Score of -0.5 (improvement) and those who withdrew, with worst score imputation had a change from baseline of 0.7 (worsening). These analyses, performed to assess the impact of withdrawals on SGRQ, suggest that placebo patients who were withdrawn had a mean worsening of the SGRQ Total Score relative to those who completed [clinstat\039.pdf:99-103, 01/31/03 clinstat\039.pdf:3859. 3866].

The average change from baseline in score for the three subscales of the SGRQ over 24 weeks of treatment is presented in table below:

NDA #21573 (12/24/02, N-000) STUDY 039: SUBSCALES OF SGRQ – CHANGES FROM BASELINE OVER 24 WEEKS IN SYMPTOMS, IMPACTS & ACTIVITIES SCORES OF THE SGRQ, ITT SAMPLE [clinstat\039.pdf:133, 491, 494, 497]√

Parameter Treatment Group	n	Change From Baseline			Comparison With Placebo		
		Mean* (SEM)	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI
SYMPTOMS SCORE							
placebo	183	-0.0 (1.4)	-2.8	2.8	--	--	--
SB 207499**	316	-5.1 (1.1)	-7.3	-2.9	-5.1	-8.4	-1.8
IMPACTS SCORE							
placebo	181	0.6 (1.0)	-1.3	2.5	--	--	--
SB 207499**	310	-3.1 (0.8)	-4.6	-1.6	-3.7	-5.9	-1.5
ACTIVITIES SCORE							
placebo	181	0.1 (1.0)	-1.9	2.1	--	--	--
SB 207499**	310	-4.1 (0.8)	-5.7	-2.4	-4.1	-6.5	-1.8

NDA #21573 (12/24/02, N-000) STUDY 039: SUBSCALES OF SGRQ – CHANGES FROM BASELINE OVER 24 WEEKS IN SYMPTOMS, IMPACTS & ACTIVITIES SCORES OF THE SGRQ, ITT SAMPLE [clinstat\039.pdf:133, 491, 494, 497]√							
Parameter		Change From Baseline			Comparison With Placebo		
Treatment Group	n	Mean* (SEM)	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI
* Mean values are adjusted for center and week. ** The dosage of SB 207499 is 15 mg. twice daily.							

Averaged over 24 weeks in the SB 207499 group, there was improvement (decrease) from baseline in the mean Symptoms, Impacts and Activities Scores of the SGRQ (-5.1, -3.1, -4.1 points, respectively). In the placebo group, there were slight worsening (increases) in the mean Symptoms, Impacts and Activities Scores of the SGRQ from baseline averaged over 24 weeks (0.0, 0.6, 0.1 points, respectively). The mean differences between treatment groups in changes from baseline of the Symptoms, Impacts and Activities Scores of the SGRQ favored the SB 207499 group over placebo (by -5.1, -3.7, -4.1 points, respectively) [clinstat\039.pdf:133]. These data show that the superiority of the SGRQ in the SB 207499 group, compared to the placebo group, was more or less equally shared among all three domains of the SGRQ.

III.A.14.b. SECONDARY MEASURES

When averaged over 24 weeks, there was no change from baseline in the mean clinic trough FVC in the SB 207499 group and a 50 mL decrease in the placebo group [clinstat\039.pdf:103, 105]. When averaged over 24 weeks, there was a decrease (improvement) from baseline in the mean post-exercise breathlessness on the 11-point modified Borg Scale in the SB 207499 group (-0.17) and an increase in the placebo group (0.07) [clinstat\039.pdf:107, 109, 436]. When change from baseline was averaged over 24 weeks, there were comparable differences in the mean 11-point Summary Symptom Score (breathlessness on a 0-4 scale, cough and sputum production each on a 0-3 scale) in both the placebo and SB 207499 groups (-0.20 and -0.22 points, respectively). These represented approximately equally improving scores in both groups [clinstat\039.pdf:111, 113]. When change from baseline was averaged over 24 weeks, there was an increase in the mean distance walked in both treatment groups, with a greater increase in the SB 207499 group (14.2 m) than the placebo group (6.3 m). This should be viewed in the context of the baseline walking distance of about 345 m for both groups [clinstat\039.pdf:115, 117]. Three levels of exacerbations were defined in the protocol to address mandatory withdrawal, but the exact prospective definition of the endpoint "COPD exacerbations" was never supplied; e.g., level, completers or all, etc. That said, there was a difference in the percent of patients who were exacerbation-free at 24 weeks between the two treatment groups, with 74.0% and 62.4% of patients in the SB 207499 and placebo groups, respectively who were exacerbation-free at 24 weeks. Percent predicted $FEV_{1.0}$, gender and smoking status were all significant risk factors for COPD exacerbations, whereas age was not. The risk of COPD exacerbation increased by 10% for every 10% reduction in percent-predicted $FEV_{1.0}$. Somewhat counter-intuitively, males had a 88% lower risk than females and smokers had a 46% lower risk than non-smokers for COPD exacerbations [clinstat\039.pdf:119, 01/31/03 039.pdf:2043-4].

III.A.14.c. TERTIARY MEASURES

The use of albuterol on an "as-needed" basis and the symptom-free days were analyzed as tertiary efficacy parameters and are presented here because they are usually-reviewed outcomes with some direct clinical relevance. At baseline, both treatment groups used similar amounts of albuterol, 3.56 puffs/day in the placebo group and 3.63 puffs/day in the SB 207499 group. There were only small changes in the use of albuterol when averaged over 24 weeks, with a mean increase of 0.24 puffs/day in the placebo group and 0.09 puffs/day in the SB 207499 group. One of the two lots of rescue medication supplied to the sites was recalled by the manufacturer after the completion of the study because of "the remote possibility" that some canisters may not have contained medication. None of the patients in the study reported problems with their albuterol inhalers. However, this introduces uncertainty about whether some, or all, of the rescue medication was actually a placebo. Overall, patients receiving placebo had 1.1% symptom-free days and patients receiving SB 207499 had 1.7% symptom-free days. This would amount to a difference of one symptom-free day over a 168-day, 24-week follow-up between the treatment groups [clinstat\039.pdf:132, 457, 530].

At Baseline and Week 24, spirograms were assessed before the first dose of double-blind study medication; 1, 2, 3, and 4 hours after the dose of double-blind study medication; and 30 (± 5) minutes after administration of 4 puffs of albuterol (360 mcg via MDI with a spacer) [clinstat\039.pdf:49]. The results of the first dose over the first four hours show that the $FEV_{1.0}$ declined by 40 mL in the placebo group and by 20 mL in the SB 207499 group. Following albuterol administration, the $FEV_{1.0}$ increased from the pre-treatment (4-hour) value by 170 mL in the placebo group and by 170 mL in the SB 207499 group.

NDA #21573 (12/24/02, N-000) STUDY 039: MEAN CHANGE FROM BASELINE IN $FEV_{1.0}$ (L) AFTER THE FIRST DOSE OF DOUBLE-BLIND MEDICATION – ITT POPULATION [clinstat\039.pdf:126]

Time	Placebo		SB 207499	
	n	Assessment Mean (SD)	n	Assessment Mean (SD)
baseline	214	1.42 (0.04)	429	1.33 (0.03)
1 hour	214	1.43 (0.04)	428	1.34 (0.03)
2 hours	213	1.40 (0.04)	422	1.34 (0.03)
3 hours	213	1.37 (0.04)	414	1.31 (0.03)
4 hours	209	1.38 (0.04)	409	1.31 (0.03)
30 min. after albuterol	210	1.55 (0.04)	413	1.48 (0.03)
Mean values are adjusted for center.				

Over the first four hours after the last dose of study medication, the $FEV_{1.0}$ was unchanged in both treatment groups. Following albuterol administration, the $FEV_{1.0}$ increased from the pre-treatment (4-hour) value by 150 mL in the placebo group and by 170 mL in the SB 207499 group.

NDA #21573 (12/24/02, N-000) STUDY 039: MEAN CHANGE FROM BASELINE IN $FEV_{1.0}$ (L) AFTER THE LAST DOSE OF DOUBLE-BLIND MEDICATION – ITT POPULATION [clinstat\039.pdf:129]				
Time	Placebo		SB 207499	
	n	Assessment Mean (SD)	n	Assessment Mean (SD)
baseline	163	1.38 (0.05)	292	1.35 (0.04)
1 hour	162	1.38 (0.05)	291	1.37 (0.04)
2 hours	162	1.38 (0.05)	289	1.37 (0.04)
3 hours	158	1.38 (0.05)	284	1.36 (0.04)
4 hours	155	1.38 (0.05)	278	1.35 (0.04)
30 min. after albuterol	156	1.53 (0.05)	283	1.52 (0.04)
Mean values are adjusted for center.				

III.A.15. SAFETY

The safety data from this study will be included in the Integrated Summary of Safety.

III.B. PROTOCOL CPMS-042

A Randomized, 24-week, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Ariflo (SB 207499, 15 mg Twice Daily) in Patients with Chronic Obstructive Pulmonary Disease (COPD)

III.B.1. LOCATIONS & DATES

The study was conducted at 98 centres in Australia and New Zealand, Germany, Spain, South Africa and the UK. The first dose of single-blind medication was taken on 16 November 1998. The first and last doses of double-blind medication were administered on 9 December 1998 and 2 December 1999, respectively [clinstat\042.pdf:3].

III.B.2. SUMMARY

This was a Phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel-group study in patients with COPD, as defined by American Thoracic Society (ATS) guidelines. Patients had at least 11 visits over a 28-week period (Week –4, Screening, through Week 24). The study began with a 4-week, single-blind, placebo run-in period, after which eligible patients were randomized to receive either SB 207499 or matching placebo in a ratio of 2:1 for 24 weeks. One tablet of SB 207499 or matching placebo was taken twice daily, immediately after breakfast and after the evening meal. Albuterol MDI was used as rescue medication. This study was a duplicate of study 039 in all ways that affected efficacy but did not include pharmacokinetic sampling.

The primary efficacy endpoints were change from baseline in trough forced expiratory volume in one second ($FEV_{1.0}$) and change from baseline in total score of the St George's Respiratory Questionnaire (SGRQ). The primary comparison was the average difference between the SB 207499 treatment group and the placebo treatment group over the 24 weeks of the double-blind period.

Patients failing to complete the double-blind period were more frequent in the SB 207499 treatment group (25.7%) than in the placebo group (22.6%). This was largely due to premature discontinuations because of adverse events (SB 207499 15.0%, placebo 9.7%) and most of these were not due to COPD exacerbations (SB 207499 12.9%, placebo 7.5%). Withdrawals from the SB 207499 group due to gastrointestinal complaints occurring during the double-blind treatment period were more common with the experimental treatment (SB 207499 6.8%, placebo 0.9%). All percentages are based on the numbers of patients randomized to each treatment group. Compliance with the experimental treatment was 92.6% for patients assigned to SB 207499 and was 98.2% for patients assigned to placebo. Concomitant medications were used to treat COPD

exacerbations in 28.3% of placebo patients and in 27.4% of SB 207499 patients. Of patients who required concomitant medications to treat exacerbations of COPD, a greater percent of placebo patients (43.8%) than SB 207499 patients (39.2%) used prednisolone, prednisone, methylprednisolone or deflazacort (systemic corticosteroids).

When averaged over 24 weeks of treatment and compared to baseline in a repeated measures analysis, there was a 30 mL increase in mean clinic trough $FEV_{1.0}$ in the SB 207499 group and no change in the placebo group. The improvement in mean trough $FEV_{1.0}$ in the SB 207499 group increased slowly over 12 weeks before stabilizing. The difference between treatments was not statistically significant. In the SB 207499 treatment group, the total score of the SGRQ decreased (improved) from baseline at Week 12, and did not further change at week 24. The placebo group showed a greater mean decline (improvement) in the total score of the SGRQ than did the SB 207499 group and the two treatments were not statistically separable. The improvement in the SGRQ was consistent and about equal over all three domains for both treatments, again favoring a slight superiority of the placebo. Very minor changes in secondary and tertiary endpoints were fairly well balanced with regard to the efficacy of both treatments, about half of the endpoints favoring the efficacy of each treatment.

After the first dose of study medication, neither treatment group showed evidence of an acute effect over the subsequent four hours. No enhancement of albuterol-induced bronchodilation over the 30 minutes following the 4-hour post-first-dose spirogram was apparent in either treatment group. Over the first four hours, after the last dose of study medication, the $FEV_{1.0}$ decreased by 20 mL in the placebo group and decreased by 10 mL in the SB 207499 group. Following albuterol administration, the $FEV_{1.0}$ increased from the pre-treatment (4-hour) value by 140 mL in the placebo group and by 150 mL in the SB 207499 group. There was neither a first-dose effect, a last-dose effect nor enhancement of albuterol-induced bronchodilation after either.

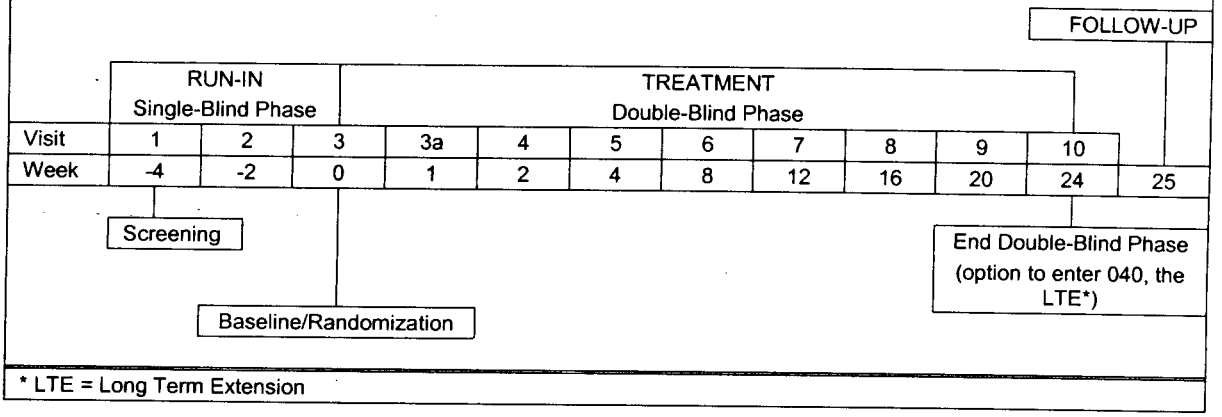
III.B.3. OBJECTIVE

The primary objective was to demonstrate the clinical efficacy of oral SB 207499 (15 mg bid) versus placebo by assessment of forced expiratory volume in 1 second ($FEV_{1.0}$) and by total score of the St George's Respiratory Questionnaire over 24 weeks in patients with COPD [clinstat\042.pdf:1637].

III.B.4. DESIGN

The design of this protocol was identical to protocol 039 with a couple of exceptions. No blood samples were drawn in this trial for pharmacokinetic analysis and those patients who complete study 042 according to the protocol (ie up to week 24), had the option of entering a different open label long term extension (LTE) study, SB 207499/040 [clinstat\042.pdf:1638-9, 1641].

NDA #21573 (12/24/02, N-000) STUDY 042: SCHEMATIC REPRESENTATION OF STUDY DESIGN [clinstat\042.pdf:1639]√



III.B.5. PATIENTS

Patient inclusion, exclusion, compliance and randomization criteria for this trial were identical to the criteria for study 039 with two exceptions. Patients were who had the clinical diagnosis of COPD, were defined by the European Respiratory Society Guidelines as stated in European Union Committee for Proprietary Medicinal Product for European multi-national studies (Siafakis NM, Vermeire P, Pride NB, *et al.* 1995. ERS Consensus Statement: Optimal Assessment and Management of Chronic Obstructive Pulmonary Disease (COPD). *Eur Respir J,* 8, 1398-1420). To be included in this trial (042) patients had to have fixed airway obstruction defined as the degree of $FEV_{1.0}$ response to 400 mcg of salbutamol by means of an MDI with a spacer, instead of 180 mcg in 039 and 156 [clinstat\042.pdf:33, 203, 1643-45, 1655, 1984-6].

III.B.6. TREATMENT

The treatment is the same as in study 039, with the exception of the batch numbers of the active treatment and the placebo.

NDA #21573 (12/24/02, N-000) STUDY 042: APPEARANCE, FORMULATION AND BATCH NUMBERS OF STUDY MEDICATION [clinstat\042.pdf:35]√

Study Drug	Appearance	Formulation	Dose	Batch Number
SB 207499	off-white, round, convex	tablet	15 mg	U97093, U98019
placebo	off-white, round, convex	tablet	--	U97090, U98102

Appendix A contains the Certificate of Analysis [clinstat\042.pdf:2418].

Prior, treatment, allowed and prohibited medications for this study (042) were the same as for study 039. The use of salbutamol 100 ug/actuation, 200 actuations per canister (MDI with or without a spacer) on an "as-needed" (prn) basis was permitted throughout the study and recorded every evening in the diary card. Ventolin was provided by local SB offices to the participating centers in Australia and New Zealand, South Africa and Spain. Sultanol. was provided by the local SB office to the

participating centres in Germany. Ventolin. was provided centrally to the participating centers in the UK. If the patient experienced symptoms which did not respond adequately to rescue medication (e.g., salbutamol, 2 actuations every 4 hours), the patient was to contact the Investigator. If a patient occasionally used salbutamol at an interval of less than every 4 hours (did not exceed twice a day at the reduced interval), the patient remained in the trial at the discretion of the Investigator [clinstat\042.pdf:35-8, 1687-8].

III.B.7. VARIABLES

The parameters that were measured are the same in this trial (042) as they were in protocol 039, except that pharmacokinetic samples will not be collected or, obviously, measured [clinstat\042.pdf:1671-80].

III.B.8. PROCEDURE FLOW CHART

NDA #21573 (12/24/02, N-000) STUDY 042: PROCEDURE FLOW CHART [clinstat\042.pdf:1641-2]													
	Screen		Base-line								End DB	Early W/D[1]	Safety F/U[2]
Visit	1	2	3	3a	4	5	6	7	8	9	10		
Week	-4	-2	0	+1	+2	+4	+8	+12	+16	+20	+24		+25
medical & surgical history	X												
PA chest radiograph[16]	X												
TLCO[3]	X												
pulmonary history & symptoms	X												
medication history	X												
St. George's Respiratory Questionnaire (SGRQ)[18]			X					X			X	X	
SF-36			X								X	X	
study medication compliance		X	X	X	X	X	X	X	X	X	X	X	
concomitant medications/procedures		X	X	X	X	X	X	X	X	X	X	X	X
baseline signs, symptoms & adverse events		X	X	X	X	X	X	X	X	X	X	X	X
exacerbation assessment/resource use	X	X	X	X	X	X	X	X	X	X	X	X	X
overall breathlessness (modified Borg Scale)	X	X	X		X	X	X	X	X	X	X		
diary card review		X	X	X	X	X	X	X	X	X	X	X	
physical examination (PE)[4]	X		X								X	X	X[5]
vital signs (BP, HR)	X[6]	X	X[6]	X	X	X	X	X	X	X	X[6]	X[6]	X
resting 12-lead electrocardiogram (ECG)	X		X[12]	X	X	X	X	X	X	X	X[12]	X	X[5]
Holter monitoring[7]		X		X						X			
exercise tolerance (6-minute walk)	X	X	X			X	X	X	X	X	X		
post-exercise SaO_2 & breathlessness	X	X	X			X	X	X	X	X	X		
albuterol reversibility [8]	X												
pulmonary functions (PFTs) without albuterol[9]		X	X		X	X	X	X	X	X	X	X	X
hourly PFTs for 4 hours post first & last dose[10]			X								X		
laboratory tests	X[15, 20]		X	X	X	X	X	X	X[11]	X[11, 15]	X	X[15]	X[5, 11]
arterial blood gas (ABG) & SaO_2 [13]			X								X		

1. Patients who stop taking study medication between clinic visits will attend the clinic within 24 hours for an early withdrawal visit.
2. Patients who enter the open-label extension study do not require a final safety follow-up visit.
3. TLCO will be performed at Visit 1 if not performed during the previous 24 weeks or if the results are unavailable. Alternatively, TLCO may be scheduled between Visits 1 and 3.
4. To include a respiratory examination.
5. If abnormalities at previous visit

6. Blood pressure/heart rate measured after 5 minutes sitting and then orthostatic blood pressure/heart rate measured in supine position for 5 minutes and then sitting with legs dependent for one minute. Orthostatic vital signs will also be measured at any gastrointestinal adverse experience follow-up.
7. In 100 patients at selected sites. Holter monitoring for 48 hours at Visit 2 and for 24 hours at Visits 3a and 9.
8. Before and 30 minutes (± 5) after administration of 400 mcg salbutamol via a MDI with a spacer (reversibility and % predicted FEV).
9. Includes FEV1, FEV6, FVC, FEF25-75, FEF75, PEFR measured by centralized spirometry by the same person at each visit.
10. Pulmonary function tests 30 minutes (?5) after salbutamol following the 4-hour post-dose assessment at Visits 3 and 10.
11. Urinary beta-HCG tests will be performed in females of childbearing potential. No other laboratory samples will be collected at Visits 8 and 9.
12. Additional 12-lead ECG at Cmax (i.e., 3 hours post dose of study medication) at visits 3 and 10.
13. In patients with < 40% of predicted FEV1 at Visit 1 only (optional).
14. Re-dispense the same study medication bottle dispensed at Visit 3.
15. Three faecal occult blood specimens will be requested between visits 1 and 3, between visits 9 and 10, and following early withdrawal. Further specimen (s) at a gastrointestinal adverse experience follow up.
16. Postero-anterior chest radiograph should be performed within 12 weeks before Visit 3 (Baseline) and the results must be available to the investigator at Visit 3.
17. To be completed at the time of withdrawal or at study conclusion.
18. To be completed if the patient withdraws at a scheduled visit (if the visit is other than visit 3, 7 or 10).
19. In addition to the specified blood chemistry analytes, amylase will also be measured at baseline (visit 3) and at any gastrointestinal adverse experience follow up.
20. Includes a separate blood sample that will be collected for DNA extraction (procedure is optional). If patient has completed screening prior to this amendment, blood may be collected at patient's next visit which includes a routine blood draw for haematology and clinical chemistry (Visits 3 to 7, 10).

III.B.9. STATISTICS

In order to obtain 450 evaluable patients this study will enroll approximately 645 patients in a ratio of 2:1 for SB 207499 to placebo. Assuming a standard deviation of 12 units in the total score of the SGRQ, there is at least 90% power to detect a 4-unit (empirically defined as the minimum clinically relevant difference) difference in the average of the 12- and 24-week assessments at an adjusted significance level of 0.025. For $FEV_{1.0}$ there will be at least 90% power to detect a clinically relevant difference of 120 ml assuming a standard deviation of 270 ml and the same significance level.

The primary comparison will be the average difference between the SB 207499 treatment group and the placebo treatment group over the 24 weeks of the double-blind period. Secondary comparisons of interest will be the comparison between groups at Week 24 and the comparison of groups at endpoint. Endpoint of treatment is defined as the last observation for a patient in the double-blind period. Additional comparisons between treatment groups will be made for pulmonary function tests at 1, 2, 3, 4 hours and 30 minutes post-salbutamol inhalation after the first and last doses of SB 207499 and for all efficacy variables at Weeks 2, 4 , 8, 12, 16, 20 and 24 of the double-blind period.

The modified intent-to-treat population will include all patients who receive randomized study medication, have a baseline efficacy evaluation and at least one efficacy evaluation during the double blind period. Data collected more than one day after the last dose of study medication in the double blind period will be excluded from the analysis. The modified intent-to-treat population is the primary population in this study.

In all statistical models used in the analysis of modified intent-to-treat and per protocol populations described above where the effect of country is present, countries enrolling less than 6 patients will be combined. Descriptive statistics will be provided for all demographic and baseline characteristics. All linear models to assess treatment effects for efficacy measures will be performed using SAS PROC MIXED.

The assessment of treatment differences for the primary efficacy variables will be based on a repeated measures model with effects for treatment, country and time. Age, gender and smoking status may also be included in the model as covariates. Several correlation structures will be explored including compound symmetry, unstructured and spatial correlation. Prior to testing for the average treatment effect over 24 weeks, a full model will be examined to test for treatment-by-country interaction, treatment-by-time interaction and time-by country interaction. Each interaction effect will be tested at a significance level of 0.10. If evidence of a treatment-by-country interaction is found exploratory analyses will be undertaken to describe the nature of the interaction and results will be presented by country. If evidence of a treatment-by-time interaction is found, exploratory analyses will be undertaken to describe the nature of the interaction.

The durability of treatment effect will be further assessed using repeated measures models which give more weight to data collected in the latter part of the study.

If no evidence of interactions is observed the test for the average treatment effect over 24 weeks will be based on a reduced model with all interaction effects removed. Least squares means along with associated 95% confidence intervals will be calculated for each treatment group. Least squares means and ninety-five percent (95%) confidence intervals will also be calculated for the treatment difference. Differences between treatment groups will be assessed using T-tests on the least square means. To control the overall type I error the significance level in the test for treatment differences in the primary endpoints will be adjusted using the modified Bonferroni procedure of Hochberg.

Normality assumptions will be assessed by graphical analyses of marginal residuals at each visit. If gross violations from normality are evident, the method of Generalized Estimating Equations will be used to confirm the inference from the mixed model procedure. All repeated measures analyses will be based on available data only. Missing data will not be imputed and will be assumed missing completely at random. This assumption will be examined using exploratory analyses to describe the response in the population of patients terminating the study prematurely [clinstat\042.pdf:1703-5].

III.B.10. DISPOSITION

The number of patients who entered the single-blind period, were randomized to receive study medication, completed the study, were eligible for analyses, and who entered the open-label extension study are presented in the following table:

NDA #21573 (12/24/02, N-000) STUDY 042: PATIENT DISPOSITION [clinstat\042.pdf:72, 215-6, 232]√			
	Treatment Group		
Disposition	Placebo n (% of randomized)	SB 207499 (15 mg bid) n (%of randomized)	Total n (%of randomized)
entered single-blind phase	--	--	979
randomized	226 (100.0)	474 (100.0)	700 (100.0)
withdrawn from double-blind phase	51 (22.6)	122 (25.7)	173 (24.7)
ITT efficacy analysis	219 (96.9)	440 (92.8)	659 (94.1)
PP efficacy analysis	198 (87.6)	392 (82.7)	590 (84.3)
completed double-blind phase	175 (77.4)	352 (74.3)	527 (75.3)
entered open-label extension (LTE)	145 (64.2)	282 (59.5)	427 (61.0)

In the table that follows, patients failing to complete the double-blind period were slightly more frequent in the SB 207499 treatment group (25.7%) than in the placebo group (22.6%). This is not as dramatic as findings in study 039 but is in the same direction.

NDA #21573 (12/24/02, N-000) STUDY 042: REASON FOR EARLY TERMINATION BY TREATMENT GROUP [clinstat\042.pdf:74, 232]√		
	Treatment	
Withdrawal Reason	Placebo (n = 226) n (%)	SB 207499 (n = 474) n (%)
adverse events*	22 (9.7)	71 (15.0)
COPD exacerbation	5 (2.2)	10 (2.1)
not due to a COPD exacerbation	17 (7.5)	61 (12.9)
protocol deviation, including non-compliance	20 (8.8)	25 (5.3)
lost to follow-up	6 (2.7)	13 (2.7)
insufficient therapeutic effect	2 (0.9)	5 (1.1)
other	1 (0.4)	8 (1.7)
total withdrawn prematurely	51 (22.6)	122 (25.7)
completed double-blind phase	175 (77.4)	352 (74.3)
* Adverse event row includes COPD exacerbations.		

The most frequent reason for early termination in both treatment groups was "adverse events" which were about 1/2 more frequent in the SB 207499 group than in the placebo group (SB 207499 15.0%, placebo 9.7%). Premature discontinuations because of adverse events attributable to something other than "COPD exacerbation" were also more frequent in the SB 207499 group than in the placebo group (SB 207499 12.9%, placebo 7.5%). Withdrawals from the SB 207499 group due to gastrointestinal complaints occurring during the double-blind treatment period were more common with the experimental treatment (SB 207499 6.8%, placebo 0.9%) [clinstat\042.pdf:139-43]. All percentages are based on the numbers of patients randomized to each treatment group. These findings were similar in direction to findings in the study 039.

III.B.11. DEMOGRAPHICS

Like most pharmaceutical studies, this was almost exclusively a trial conducted in Caucasians. Males were the most frequent gender in both treatment groups. The dominant age range of patients enrolled in this COPD study was over 50, with a mean of 65 years. By inspection, the medians are very close to the means which suggests a fairly symmetrical distribution without much skewness. The frequencies of most characteristics were fairly evenly distributed between treatment groups. Other baseline demographic characteristics of interest are shown in the following table [clinstat\042.pdf:80, 240].

NDA #21573 (12/24/02, N-000) STUDY 042: DEMOGRAPHIC CHARACTERISTICS AT SCREENING (ALL RANDOMIZED PATIENTS) [clinstat\042.pdf:80, 83, 240, 243]√					
		Treatment Group			
		Placebo n = 226		SB 207499 15 mg bid n = 474	
Characteristic		n	(%)	n	(%)
Sex	Female	46	(20.4)	92	(19.4)
	Male	180	(79.6)	382	(80.6)
Race	Caucasian	224	(99.1)	471	(99.4)
	Oriental	2	(0.9)	2	(0.4)

NDA #21573 (12/24/02, N-000) STUDY 042: DEMOGRAPHIC CHARACTERISTICS AT SCREENING (ALL RANDOMIZED PATIENTS) [clinstat\042.pdf:80, 83, 240, 243]√					
		Treatment Group			
		Placebo n = 226		SB 207499 15 mg bid n = 474	
Characteristic		n	(%)	n	(%)
	Other*	0	(0.0)	1	(0.2)
Age, years	< 50	9	(4.0)	21	(4.4)
	50 - 65	108	(47.8)	216	(45.6)
	> 65	109	(48.2)	237	(50.0)
	Mean (SD)	64.7 (8.5)		64.5 (8.1)	
	Median	65		65.5	
	Min, Max	41, 80		40, 82	
Weight, kg.	Mean (SD)	75.0 (15.0)		73.9 (14.1)	
	Min, Max	40, 124		39, 134	
$FEV_{1.0}$ (L)	Mean (SD)	1.45 (0.43)		1.44 (0.42)	
	Min, Max	0.56, 2.93		0.49, 2.77	
Reversibility (%)	Mean (SD)	4.9 (8.6)		5.2 (9.0)	
	MIN, MAX	-43.7, 27.0		-42.0, 49.1	
* not further defined					

III.B.12. COMPLIANCE WITH TREATMENT

As stipulated in the protocol, patients were to be withdrawn from the study if study medication compliance at each visit during the double-blind period was not $\geq$ 80% and $\leq$ 120%. Overall compliance was more than 90% in both groups with a slightly higher proportion of patients with 80-120% compliance in the placebo group than in the SB 207499 group (98.2% vs. 92.6%) [clinstat\042.pdf:90-1].

NDA #21573 (12/24/02, N-000) STUDY 042: COMPLIANCE WITH TREATMENT [clinstat\042.pdf:91]√		
Compliance (%)	Treatment	
	Placebo (N = 226) n (%)	SB 207499 15 mg BID (N = 474) n (%)
< 80	4 (1.8)	31 (6.6)
80 - 120	220 (98.2)	436 (92.6)
> 120	0	4 (0.8)
mean (SD)	98.0 (5.4)	95.6 (12.0)
Min, Max	68.7, 117.2	7.1, 186.7
Compliance data were available for 224 patients in the placebo group and 471 patients in the SB 207499 group.		

III.B.13. CONCOMITANT COPD MEDICATION USE

In general, there were no marked differences between the treatment groups in the receipt of medication for exacerbations of COPD. The most frequently received medications were amoxycillin (5.3% and 6.3% of patients receiving placebo and SB 207499, respectively) and, in the placebo group, prednisolone (5.3% of patients) and, in

the SB 207499 group, paracetamol (3.8% of patients). Of patients who required concomitant medications to treat exacerbations of COPD, a greater percent of placebo patients (43.8%) than SB 207499 patients (39.2%) used prednisolone, prednisone, methylprednisolone or deflazacort (systemic corticosteroids) [clinstat\042.pdf:90].

NDA #21573 (12/24/02, N-000) STUDY 042: CONCOMITANT COPD MEDICATION USE [clinstat\042.pdf:90]√		
COPD Medication	Treatment	
	Placebo (N = 226) n (%)	SB 207499 15 mg BID (N = 474) n (%)
TOTAL*	64 (28.3)	130 (27.4)
amoxycillin	12 (5.3)	30 (6.3)
paracetamol	6 (2.7)	18 (3.8)
prednisolone	12 (5.3)	17 (3.6)
prednisone	6 (2.7)	13 (2.7)
clavulanic acid	5 (2.2)	13 (2.7)
cefuroxime	8 (3.5)	12 (2.5)
methylprednisolone	8 (3.5)	11 (2.3)
deflazacort	2 (0.9)	10 (2.1)
azithromycin	8 (3.5)	9 (1.9)
salbutamol	6 (2.7)	8 (1.7)
ciprofloxacin	6 (2.7)	7 (1.5)
ipratropium	7 (3.1)	6 (1.3)
* Total represents total number of patients receiving concomitant medication.		

III.B.14. EFFICACY

III.B.14.a. PRIMARY MEASURES

The difference between treatments in the $FEV_{1.0}$ mean change from baseline is shown in the following table. There was no mean change from baseline in the placebo group and the SB 207499 group showed a mean increase over the 24 weeks of 30 mL. Hence, the difference in mean changes from baseline between groups was also 30 mL, which was not statistically significant when corrected for multiple endpoints by the modified Bonferroni procedure of Hochberg [clinstat\042.pdf:93, 1705].

NDA #21573 (12/24/02, N-000) STUDY 042: SUMMARY OF DIFFERENCE BETWEEN TREATMENTS IN AVERAGE CHANGE FROM BASELINE OVER 24 WEEKS (REPEATED MEASURES ANALYSIS) IN TROUGH $FEV_{1.0}$ (L) – ITT GROUP [clinstat\042.pdf:93, 362]√									
Treatment Group	N	Change From Baseline				Comparison With Placebo			
		Mean*	SEM	Lower 95% CI	Upper 95% CI	Mean Diff.	Lower 95% CI	Upper 95% CI	Type I Error
placebo	219	-0.00	0.02	-0.03	0.03	--	--	--	--
SB 207499	440	0.03	0.01	0.00	0.05	0.03	0.00	0.06	0.044
* Mean values are adjusted for country and week.									

The numbers of patient in the two treatment groups were fewer than the number who were randomized (placebo = 226, SB 207499 = 474). This means that either these patients failed to provide a baseline spirometry or dropped out before the first post-treatment spirometry was determined [7/9/03 Teleconference, 03-07-09_Tel.pdf].

The individual means in trough $FEV_{1.0}$ at each visit are shown in the table below from which the average change from baseline for the two treatments was calculated. The table shows that the improvement in the SB 207499 group trough $FEV_{1.0}$ increased slowly over 12 weeks before stabilizing at it's maximum of about 50 mL.

NDA #21573 (12/24/02, N-000) STUDY 042: MEAN TROUGH $FEV_{1.0}$ (L) IN THE ITT POPULATION BY VISIT AND TREATMENT GROUP [clinstat\042.pdf:94, 363]√

Week	SB 207499		Placebo	
	N	Mean* (SEM)	N	Mean* (SEM)
Baseline	448	1.37 (0.03)	220	1.35 (0.03)
2	439	1.39 (0.03)	219	1.34 (0.04)
4	423	1.40 (0.03)	208	1.35 (0.04)
8	400	1.41 (0.03)	197	1.34 (0.04)
12	385	1.42 (0.03)	189	1.34 (0.04)
16	378	1.43 (0.03)	187	1.35 (0.04)
20	368	1.42 (0.03)	182	1.35 (0.04)
24	348	1.42 (0.04)	177	1.35 (0.04)
Endpoint	448	1.41 (0.03)	220	1.35 (0.04)

* mean values were adjusted for country

The SGRQ has a 100 point scale size (lower scores represent greater wellness), is divided into three domains and a minimum important difference of four units [www.atsqol.org most recent update April 2002]. As before, the numbers of patient in the two treatment groups were fewer than the numbers who were randomized. This means that either these patients failed to provide a baseline SGRQ or dropped out before the first post-treatment SGRQ was determined [7/9/03 Teleconference, 03-07-09_Tel.pdf]. In the following table, the placebo group showed an average decrease (improvement) from baseline that was actually superior to that shown by SB 207499. In this study, SGRQ, the co primary endpoint, failed rather dramatically to show any effect of SB 207499.

NDA #21573 (12/24/02, N-000) STUDY 042: SUMMARY OF DIFFERENCE BETWEEN TREATMENTS IN AVERAGE CHANGE FROM BASELINE OVER 24 WEEKS (REPEATED MEASURES ANALYSIS) IN SGRQ TOTAL SCORE – ITT GROUP [clinstat\042.pdf:96, 362]√

Treatment Group	N	Change From Baseline				Comparison With Placebo			
		Mean*	SEM	Lower 95% CI	Upper 95% CI	Mean Diff.	Lower 95% CI	Upper 95% CI	Type I Error
placebo	190	-4.9	1.0	-6.8	-3.0	--	--	--	--
SB 207499	375	-4.2	0.8	-5.7	-2.6	0.7	-1.5	2.9	0.473

* Mean values were adjusted for country and week.

The mean SGRQ values for each treatment at each visit at which they were determined is shown in the following table and reiterates the findings of the last table.

NDA #21573 (12/24/02, N-000) STUDY 042: MEAN SGRQ (TOTAL SCORE) IN THE ITT POPULATION BY VISIT AND TREATMENT GROUP [clinstat\042.pdf:98, 378]√

Week	SB 207499		Placebo	
	N	Mean* (SEM)	N	Mean* (SEM)
Baseline	406	43.9 (1.1)	202	46.0 (1.4)

NDA #21573 (12/24/02, N-000) STUDY 042: MEAN SGRQ (TOTAL SCORE) IN THE ITT POPULATION BY VISIT AND TREATMENT GROUP [clinstat\042.pdf:98, 378]√				
	SB 207499		Placebo	
Week	N	Mean* (SEM)	N	Mean* (SEM)
12	364	39.7 (1.2)	185	41.5 (1.5)
24	339	39.5 (1.4)	173	40.7 (1.7)
Endpoint	406	40.6 (1.3)	202	41.8 (1.6)
* mean values were adjusted for country				

The average change from baseline in score for the three subscales of the SGRQ over 24 weeks of treatment is presented in table below and shows that the slight superiority of placebo was apparent over all three domains.

NDA #21573 (12/24/02, N-000) STUDY 042: SUBSCALES OF SGRQ – MEAN CHANGES FROM BASELINE OVER 24 WEEKS IN SYMPTOMS, IMPACTS & ACTIVITIES SCORES OF THE SGRQ, ITT SAMPLE [clinstat\042.pdf:119, 444, 447, 450]√							
Parameter Treatment Group	n	Change From Baseline			Comparison With Placebo		
		Mean* (SEM)	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI
SYMPTOMS SCORE							
placebo	191	-6.5 (1.6)	-9.6	-3.4	--	--	--
SB 207499**	385	-7.0 (1.3)	-9.5	-4.6	-0.6	-3.7	2.5
IMPACTS SCORE							
placebo	190	-4.4 (1.1)	-6.6	-2.3	--	--	--
SB 207499**	375	-3.5 (0.9)	-5.3	-1.7	0.9	-1.2	3.1
ACTIVITIES SCORE							
placebo	190	-4.6 (1.2)	-6.9	-2.3	--	--	--
SB 207499**	375	-3.4 (1.0)	-5.3	-1.5	1.2	-1.1	3.5
* Mean values are adjusted for country.		** The dosage of SB 207499 is 15 mg. twice daily.					

III.B.14.b. SECONDARY MEASURES

When averaged over 24 weeks, there was a 20 mL increase from baseline in the mean clinic trough FVC in the SB 207499 group and a 20 mL decrease in the placebo group [clinstat\042.pdf:100, 102]. When averaged over 24 weeks, there was a decrease (improvement) from baseline in the mean post-exercise breathlessness on the 11-point modified Borg Scale in the SB 207499 group (-0.36) and a smaller decrease in the placebo group (-0.16) [clinstat\042.pdf:104-5]. When change from baseline was averaged over 24 weeks, there was a greater decline (improvement) in the mean 11-point Summary Symptom Score (breathlessness, cough and sputum production each on a 0-3 or 0-4 point scale) in the placebo group than in the SB 207499 group (-0.50 and -0.33 points, respectively) [clinstat\042.pdf:106, 108]. When change from baseline was averaged over 24 weeks, there was an increase in the mean distance walked in both treatment groups, with a greater increase in the placebo group (14.1 m) than the SB 207499 group (3.8 m). This should be viewed in the context of the baseline walking distance of about 410 m for both groups [clinstat\042.pdf:109-10]. There was a difference in the exacerbation-free survival rates between the two treatment groups, with 58.8% and 61.3% of patients in the SB 207499 and placebo groups, respectively who were exacerbation-free at 24 weeks. Percent predicted $FEV_{1.0}$ was a significant risk factor for

COPD exacerbations, whereas age, gender and baseline smoking status was not. The risk of COPD exacerbation increased by 20% for every 10% reduction in percent-predicted $FEV_{1.0}$ [clinstat\042.pdf:111].

III.B.14.c. TERTIARY MEASURES

The use of albuterol on an "as-needed" basis and the symptom-free days were analyzed as tertiary efficacy parameters and are presented here because they are usually-reviewed outcomes with some direct clinical relevance. At baseline the treatment groups had similar salbutamol usage, with a mean of 3.41 puffs/day in the placebo group and 3.28 puffs/day in the SB 207499 group. There were only small changes from baseline in salbutamol use over the study with a mean increase of 0.08 puffs/day in the placebo group and 0.06 puffs/day in the SB 207499 group. There was no difference between the treatment groups. (Overall, patients treated with placebo had a mean of 2.2% of their days symptom free (i.e., free of cough, breathlessness and sputum) compared with a mean of 3.1% of days for patients treated with SB 207499. There was no difference between the treatment groups. This would amount to 3-5 symptom-free days over a 168-day, 24-week follow-up for both treatment groups and a difference between groups of about 1.5 symptom free days [clinstat\042.pdf:118-9].

At Baseline and Week 24, spirograms were assessed before the first dose of double-blind study medication; 1, 2, 3, and 4 hours after the dose of double-blind study medication; and 30 (± 5) minutes after administration of 4 puffs of albuterol (400 mcg via MDI with a spacer) [clinstat\042.pdf:113-4]. The results of the first dose over the first four hours show that the $FEV_{1.0}$ declined by 10 mL in the placebo group and stayed the same in the SB 207499 group. Following albuterol administration, the $FEV_{1.0}$ increased from the pre-treatment (4-hour) value by 140 mL in both groups.

NDA #21573 (12/24/02, N-000) STUDY 042: MEAN CHANGE FROM BASELINE IN $FEV_{1.0}$ (L) AFTER THE FIRST DOSE OF DOUBLE-BLIND MEDICATION – ITT POPULATION [clinstat\042.pdf:114]

Time	Placebo		SB 207499	
	n	Assessment Mean (SD)	n	Assessment Mean (SD)
baseline	224	1.36 (0.03)	471	1.37 (0.03)
1 hour	224	1.37 (0.04)	471	1.39 (0.03)
2 hours	223	1.37 (0.04)	470	1.38 (0.03)
3 hours	221	1.35 (0.04)	469	1.37 (0.03)
4 hours	218	1.35 (0.04)	463	1.37 (0.03)
30 min. after albuterol	218	1.49 (0.04)	456	1.51 (0.03)
Mean values are adjusted for country.				

Over the first four hours after the last dose of study medication, the $FEV_{1.0}$ decreased by 20 mL in the placebo group and decreased by 10 mL in the SB 207499 group. Following albuterol administration, the $FEV_{1.0}$ increased from the pre-treatment (4-hour) value by 140 mL in the placebo group and by 150 mL in the SB 207499 group.

NDA #21573 (12/24/02, N-000) STUDY 042: MEAN CHANGE FROM BASELINE IN $FEV_{1.0}$ (L) AFTER THE LAST DOSE OF DOUBLE-BLIND MEDICATION – ITT POPULATION [clinstat\042.pdf:367]				
Time	Placebo		SB 207499	
	n	Assessment Mean (SD)	n	Assessment Mean (SD)
baseline	173	1.35 (0.04)	348	1.42 (0.04)
1 hour	173	1.35 (0.05)	348	1.44 (0.04)
2 hours	171	1.34 (0.05)	347	1.44 (0.04)
3 hours	171	1.33 (0.05)	347	1.42 (0.04)
4 hours	170	1.33 (0.05)	344	1.41 (0.04)
30 min. after albuterol	170	1.47 (0.05)	344	1.56 (0.04)
Mean values are adjusted for center.				

III.B.15. SAFETY

The safety data from this study will be included in the Integrated Summary of Safety.

III.C. PROTOCOL CPMS-091

A Randomized, 24-week, Double-blind, Placebo-controlled, Parallel-group Study Followed by a 2-Week, Randomized, Double-blind, Run-out Phase to Evaluate the Efficacy, Safety, Tolerability and Discontinuation of SB 207499 (15 mg Twice Daily) in Patients with Chronic Obstructive Pulmonary Disease (COPD)

III.C.1. LOCATIONS & DATES

The study was conducted at 110 centres in Belgium, Finland, France, Italy, The Netherlands, Norway, Portugal, Spain and the United Kingdom. The first dose of single-blind medication was taken on 11 December 1998. The first dose of 24-Week double-blind medication was administered on 3 January 1999 and the last dose of 2-Week double-blind run-out medication on 2 March 2000. [clinstat\091.pdf:3].

III.C.2. SUMMARY

This was a Phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel-group study in patients with COPD, as defined by American Thoracic Society (ATS) guidelines. Patients had at least 11 visits over a 28-week period (Week –4, Screening, through Week 24). The study began with a 4-week, single-blind, placebo run-in period, after which eligible patients were randomized to receive either SB 207499 or matching placebo in a ratio of 2:1 for 24 weeks. One tablet of SB 207499 or matching placebo was taken twice daily, immediately after breakfast and after the evening meal. Albuterol MDI was used as rescue medication. This study was a duplicate of study 039 in all ways that reflected efficacy, as well as measuring population pharmacokinetics. The single dissimilarity was that the 24 weeks were followed by a 2-week run-out period during which SB 207499 treated patients were re-randomized to receive either SB 207499 or placebo and further analyzed at a twelfth visit.

The primary efficacy endpoints were change from baseline in trough forced expiratory volume in one second ($FEV_{1.0}$) and change from baseline in total score of the St George's Respiratory Questionnaire (SGRQ). The primary comparison was the average difference between the SB 207499 treatment group and the placebo treatment group over the 24 weeks of the double-blind period.

Patients failing to complete the double-blind period were about as frequent in the two treatment groups (SB 207499 25.8%, placebo 26.0%). This was largely due to premature discontinuations because of adverse events (SB 207499 16.6%, placebo 13.2%) that were not due to COPD exacerbations (SB 207499 14.1%, placebo 6.6%). Withdrawals from the SB 207499 group were mostly due to gastrointestinal complaints

occurring during the double-blind treatment period (SB 207499 10.9%, placebo 1.7%). All percentages are based on the numbers of patients randomized to each treatment group. Compliance with the experimental treatment was 92.7% for patients assigned to the SB 207499 group and was 96.3% for patients assigned to placebo. Concomitant medications were used to treat COPD exacerbations in 32.6% of placebo patients and in 23.0% of SB 207499 patients. Of patients who required concomitant medications to treat exacerbations of COPD, a greater percent of placebo patients (55.7%) than SB 207499 patients (39.8%) used prednisolone, prednisone, methylprednisolone or deflazacort (systemic corticosteroids).

When averaged over 24 weeks of treatment and compared to baseline in a repeated measures analysis, there was no change in the mean clinic trough $FEV_{1.0}$ in the SB 207499 group and a 30 mL decrease in the placebo group. Reduction from baseline in the trough $FEV_{1.0}$ of the placebo group occurred over the first 2 weeks of treatment. The mean difference between treatments in $FEV_{1.0}$ as a change from baseline failed to achieve statistical significance. In both treatment groups, the mean total score of the SGRQ decreased (improved) slightly from baseline to Week 12, increasing (worsening) back to almost its baseline value at week 24. The mean change in SGRQ from baseline between treatments was not statistically significant and the difference between treatment groups did not approach the minimum important difference (SB 207499 -2.7, placebo -2.3, difference 0.4). Miniscule mean changes in secondary and tertiary endpoints mostly favored SB 207499 over placebo.

The results of the first dose over the first four hours show that the $FEV_{1.0}$ was unchanged in the placebo group and increased 10 mL in the SB 207499 group. Following albuterol administration, the $FEV_{1.0}$ increased from the pre-treatment (4-hour) value by 120 mL in the placebo group and by 140 mL in the SB 207499 group. Over the first four hours, after the last dose of study medication, the $FEV_{1.0}$ increased by 10 mL in the placebo group and increased by 20 mL in the SB 207499 group. Following albuterol administration, the $FEV_{1.0}$ increased from the pre-treatment (4-hour) value by 140 mL in the placebo group and by 170 mL in the SB 207499 group. There was no first-dose effect or last-dose effect. There was increased albuterol responsiveness seen in the SB 207499 group compared with placebo four hours after the first and last dose. There was a 10 mL decrease from week 24 over the 2-week run-out in all three treatment arms (24-week treatment/2-week run-out treatment: placebo/placebo, SB207499/placebo, SB207499/SB 207499).

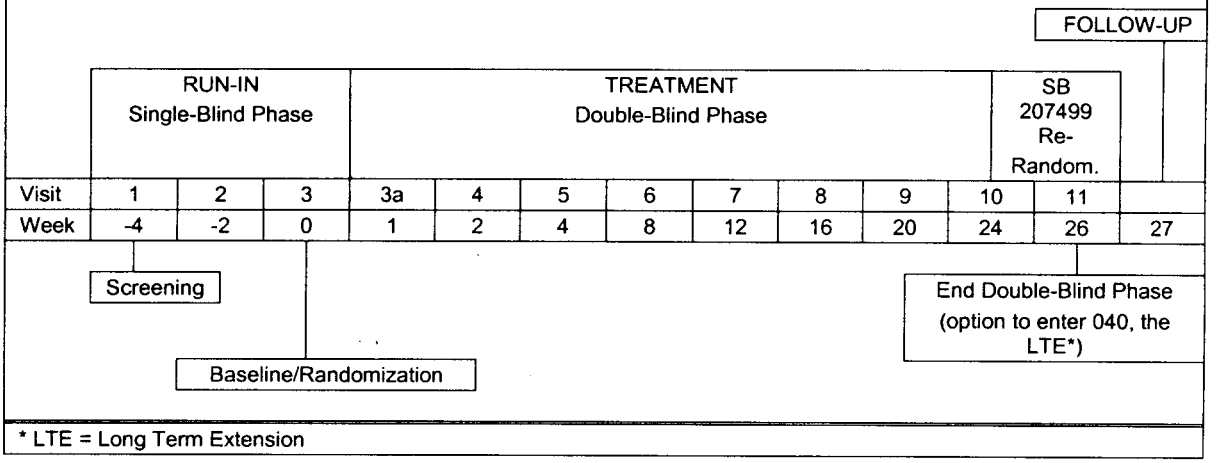
III.C.3. OBJECTIVE

The primary objective is to demonstrate the clinical efficacy of oral SB 207499 (15 mg bid) versus placebo by assessment of trough forced expiratory volume in 1 second ($FEV_{1.0}$) and by total score of the St George's Respiratory Questionnaire over 24 weeks in patients with COPD [clinstat\091.pdf:25, 2037].

III.C.4. DESIGN

The design of this protocol was identical to protocol 039 with a couple of exceptions. At the 24-week visit, patients entered a 2-Week randomized, double-blind, Run-Out phase in which patients initially randomized to SB 207499 were re-randomized to either SB 207499 15 mg or placebo twice daily. Patients initially randomized to placebo continued taking placebo. Patients were unaware that their medication was changing at Week 24. Those patients who complete study 091 according to the protocol (i.e., through week 26), had the option of entering a different open label long term extension (LTE) study, SB 207499/040, the same LTE as patients from study 042 [clinstat\091.pdf:26-30, 2038-41].

NDA #21573 (12/24/02, N-000) STUDY 091: SCHEMATIC REPRESENTATION OF STUDY DESIGN [clinstat\091.pdf:2040]



* LTE = Long Term Extension

III.C.5. PATIENTS

Patient inclusion, exclusion, compliance and randomization criteria for this trial were identical to the criteria for study 039 with one exception. To be included in this trial (091) patients had to have fixed airway obstruction defined as the degree of $FEV_{1.0}$ response to 400 mcg of salbutamol, instead of 180 mcg in 039 [clinstat\091.pdf:2044-6, 2056].

III.C.6. TREATMENT

The treatment was the same as in study 039, with the exception of the batch numbers of the active treatment and the placebo.

NDA #21573 (12/24/02, N-000) STUDY 091: APPEARANCE, FORMULATION AND BATCH NUMBERS OF STUDY MEDICATION [clinstat\091.pdf:4, 34]√

Study Drug	Appearance	Formulation	Dose	Batch Number
SB 207499	off-white, round, convex	tablet	15 mg	U97093, U98019, U99061
placebo	off-white, round, convex	tablet	--	U97090, U98018-S2, U98102

NDA #21573 (12/24/02, N-000) STUDY 091: APPEARANCE, FORMULATION AND BATCH NUMBERS OF STUDY MEDICATION [clinstat\091.pdf:4, 34]√				
Study Drug	**Appearance**	**Formulation**	**Dose**	**Batch Number**
Appendix A contains the Certificate of Analysis [clinstat\091.pdff:2932-40].				

Prior, treatment, rescue, allowed and prohibited medications for this study (091) were the same as for study 039 [clinstat\091.pdf:4, 33-7].

III.C.7. VARIABLES

The variables that were measured are the same in this trial (091) as they were in protocol 039. The only exceptions to this are the measurements of first-dose effect, last-dose effect and the measurement of these variables during the 2-week, run-out, re-randomization phase [clinstat\091.pdf:48, 2074-85].

III.C.8. PROCEDURE FLOW CHART

NDA #21573 (12/24/02, N-000) STUDY 091: PROCEDURE FLOW CHART [clinstat\091.pdf:2042-3]														
	Screen		Base -line								Start Run-Out	End Run-Out	Early W/D[1]	Safety F/U[2]
Visit	1	2	3	3a	4	5	6	7	8	9	10	11		
Week	-4	-2	0	+1	+2	+4	+8	+12	+16	+20	+24	+26		+27
medical & surgical history	X													
PA chest radiograph[16]	X													
DLCO[3]	X													
pulmonary history & symptoms	X													
medication history	X													
St. George's Respiratory Questionnaire (SGRQ)[18]			X					X			X		X	
SF-36			X								X		X	
study medication compliance		X	X	X	X	X	X	X	X	X	X	X	X	
concomitant medications/procedures		X	X	X	X	X	X	X	X	X	X	X	X	X
baseline signs, symptoms & adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X
exacerbation assessment/resource use	X	X	X	X	X	X	X	X	X	X	X	X	X	X
overall breathlessness (modified Borg Scale)	X	X	X		X	X	X	X	X	X	X	X		
diary card review		X	X	X	X	X	X	X	X	X	X	X	X	
physical examination (PE)[4]	X		X								X	X	X	X[5]
vital signs (BP, HR)	X[6]	X	X[6]	X	X	X	X	X	X	X	X[6]	X	X[6]	X
resting 12-lead electrocardiogram (ECG)	X		X[21]	X	X	X	X	X	X	X	X[21]	X	X	X[6]
Holter monitoring[7]		X		X						X				
exercise tolerance (6-minute walk)	X	X	X			X	X	X	X	X	X	X		
post-exercise SaO_2 & breathlessness	X	X	X			X	X	X	X	X	X	X		
albuterol reversibility [8]	X													
pulmonary functions (PFTs) without albuterol[9]		X	X		X	X	X	X	X	X	X	X	X	X
hourly PFTs for 4 hours post first & last dose[11]			X								X			
laboratory tests[19]	X[20, 22]		X[12]	X	X	X	X	X	X[11]	X[11, 20]	X	X	X[20]	5[5, 11]
pharmacokinetic evaluations (PK)[12]			X			X		X			X			
arterial blood gas (ABG) & SaO_2 [13]			X								X			

1. Patients who stop taking study medication between clinic visits will attend the clinic within 24 hours for an early withdrawal visit.
2. Patients who enter the open-label extension study do not require a final safety follow-up visit.
3. TLCO will be performed at Visit 1 if not performed during the previous 24 weeks or if the results are unavailable. Alternatively, TLCO may be scheduled between Visits 1 and 3.
4. To include a respiratory examination.

5. If abnormalities at previous visit
6. Orthostatic vital signs: Blood pressure and heart rate will be measured after 5 minutes sitting and then orthostatic heart rate and blood pressure will be measured by placing the patient in a supine position for 5 minutes followed by sitting with legs dependent for 1 minute. Orthostatic vital signs will also be measured at any gastrointestinal adverse experience follow-up.
7. In 100 patients at selected sites. Holter monitoring for 48 hours at Visit 2 and for 24 hours at Visits 3a and 9.
8. Before and 30 minutes (?5) after administration of 400 mcg salbutamol via an MDI with a spacer (reversibility and % predicted FEV1)
9. Includes FEV1, FEV6, FVC, FEF25-75, FEF75, and PEFR measured by centralized spirometry by the same person at each visit.
10. Pulmonary function tests 30 minutes (?5) after salbutamol following the 4-hour post-dose assessment at Visits 3 and 10.
11. Urinary beta-HCG tests will be performed in females of childbearing potential. No other laboratory samples will be collected at Visits 8 and 9.
12. Visit 5 (week +4): pre and post-dose*. Visit 7: post-dose*. Visit 10: pre-dose. (*Investigator to assign the patient to an Early/Late time interval at visit 3)
13. In patients with < 40% of predicted FEV1 at Visit 1 only (optional)
14. Re-dispense the same study medication bottle dispensed at Visit 3.
15. If a patient enters the long-term extension study, this record will be completed at Visit 11.
16. Postero-anterior chest radiograph should be performed within 12 weeks before Visit 3 (Baseline) and the results must be available to the investigator at Visit 3.
17. To be completed at the time of withdrawal or at study conclusion
18. To be completed if the patient withdraws at a scheduled visit (if the visit is other than visit 3, 7 or 10)
19. In addition to the specified blood chemistry analytes, amylase will also be measured at baseline (visit 3) and at any gastrointestinal adverse experience follow-up
20. Three fecal occult blood specimens will be requested, for collection between Visits 1 and 3, between Visits 9 and 10, and following early withdrawal. Further specimen(s) will be collected at any gastrointestinal adverse experience follow-up
21. Additional 12-lead ECG at Cmax i.e. 3 hours post-dose of study medication (at Visits 3 and 10)
22. Includes a separate blood sample that will be collected for DNA extraction (procedure is optional). If patient has completed screening prior to this amendment, blood may be collected at patient's next visit which includes a routine blood draw for hematology and clinical chemistry (Visits 3 to 7, 10, 11).

III.C.9. STATISTICS

In order to obtain 450 evaluable patients this study will enroll a total of approximately 645 patients in a ratio of 2:1 for SB-207499 to placebo. Assuming a standard deviation of 12 units in the total score of the SGRQ, there is at least 90% power to detect a 4-unit (empirically defined as the minimum clinically relevant difference) difference in the average of the 12- and 24-week assessments at an adjusted significance level of 0.025. For $FEV_{1.0}$ there will be at least 90% power to detect a clinically relevant difference of 120 ml assuming a standard deviation of 270 ml and the same significance level.

All statistical inference on clinic pulmonary function tests will based on the change from baseline, defined as the difference between the value at the evaluation of interest and the value at the pre-dose assessment at Visit 3 i.e. immediately prior to administration of double blind medication.

Several measures of efficacy will be derived from patient diary data. All diary symptom assessments will be recorded in the evening and based on observations over the course of the day. The Summary Symptom Score will be calculated as the sum of cough, sputum and breathlessness. If any of the three components are missing, the Summary Symptom Score will also be set to missing.

The percentage of days symptom free is defined as the number of days during which the patient recorded no symptoms with respect to cough, sputum and breathlessness. A symptom free day equates to a Summary Symptom Score of 0. Percent of symptom-free days will be calculated as 100 times the number of days symptom free divided by the total number days for which complete symptom data is available. Complete symptom data for a specific day is defined as a non-missing summary symptom score.

Baseline for the diary measures will be defined as the average of all available data in the 14 days prior to Visit 3. Statistical inference for all diary measures, with the exception of percentage of symptom free days, will be based on the change from baseline. The average over the 14 days immediately prior to the visit will be calculated for each patient and used as the representative score for that visit. Patients who have less than 10 days of diary data for a given visit will be excluded from the analysis for that visit. For percentage of symptom-free days the score used for analysis will be based on the percentage as calculated using all available days between pre-specified time intervals. Analyses will also be performed on the percent of days symptom-free during the entire 24-week double-blind period.

During the 24 week double-blind period, comparisons will be between the two treatments received (SB-207499 versus placebo). The SB-207499 treatment group in the

24 week double-blind period represents the combination of patients randomized to receive SB-207499 followed by placebo during the randomized Run-Out phase and patients randomized to receive SB-207499 throughout double-blind treatment. The placebo treatment group in the 24 week double-blind phase represents patients randomized to receive placebo throughout double-blind treatment.

The primary comparison will be the average difference between the SB-207499 treatment group and the placebo treatment group over the 24 week double-blind period. Secondary comparisons of interest will be the comparison between groups at Week 24 and the comparison of groups at endpoint. Endpoint of treatment is defined as the last observation for a patient in the 24-week double-blind period. Additional comparisons between treatment groups will be made for pulmonary function tests at 1, 2, 3, 4 hours and 30 minutes post-salbutamol inhalation after the first and last doses of 24-week double-blind study medication and for all efficacy variables at Weeks 2, 4 , 8, 12, 16, 20 and 24 of the 24-week double-blind period and after the 2 week randomized double-blind Run-Out period.

A comparison of pulmonary function at the end of the two week randomized Run-Out phase will be performed. Separate comparisons of the group receiving SB-207499 during the first 24 weeks followed by placebo during the randomized Run-Out phase will be made to: 1) the group of patients receiving SB-207499 throughout; and, 2) the group of patients receiving placebo throughout.

In all statistical models used in the analysis of intent-to-treat and per protocol populations described above where the effect of country is present, countries enrolling less than 6 patients will be combined. Descriptive statistics will be provided for all demographic and baseline characteristics. All linear models to assess treatment effects for efficacy measures will be performed using SAS PROC MIXED.

The assessment of treatment differences for the primary efficacy variables will be based on a repeated measures model with effects for treatment, country and time. Age, gender and smoking status may also be included in the model as covariates. Several correlation structures will be explored including compound symmetry, unstructured and spatial correlation. Prior to testing for the average treatment effect over 24 weeks, a full model will be examined to test for treatment-by-country interaction, treatment-by-time interaction and time-by c ountry interaction. Each interaction effect will be tested at a significance level of 0.10. If evidence of a treatment-by-country interaction is found, exploratory analyses will be undertaken to describe the nature of the interaction and results will be presented by country.

If evidence of a treatment-by-time interaction is found, exploratory analyses will be undertaken to describe the nature of the interaction. The durability of treatment effect will be further assessed using repeated measures models which give more weight to data collected in the latter part of the study.

If no evidence of interactions is observed the test for the average treatment effect over 24 weeks will be based on a reduced model with all interaction effects removed. Least squares means along with associated 95% confidence intervals will be calculated for each treatment group. Least squares means and ninety-five percent (95%) confidence intervals will also be calculated for the treatment difference. Differences between treatment groups will be assessed using T-tests on the least square means. To control the overall type I error, the significance level in the test for treatment differences in the primary endpoints will be adjusted using the modified Bonferroni procedure of Hochberg.

Normality assumptions will be assessed by graphical analyses of marginal residuals at each visit. If gross violations from normality are evident, the method of Generalized Estimating Equations will be used to confirm the inference from the mixed model procedure. All repeated measures analyses will be based on available data only. Missing data will not be imputed and will be assumed missing completely at random. This assumption will be examined using exploratory analyses to describe the response in the population of patients terminating the study prematurely. In addition to repeated measures, the effect of treatment at each time point will also be explored using a linear model with effects for treatment and country.

Least square means and associated 95% confidence intervals will be calculated on the change from baseline within each group and on the treatment difference. For $FEV_{1.0}$ analyses will be performed at trough and at hourly assessments following the first dose of double blind study medication. All continuous secondary and tertiary efficacy variables will be analyzed using the main effects models described above for the primary variables. Interaction terms will not be assessed for secondary and tertiary variables.

Differences between groups in time to first COPD exacerbation will be assessed using the log-rank test. The exacerbation-free survival rate at 24 weeks and associated 95% confidence intervals will be estimated for each treatment group using the Kaplan-Meier product limit. Additionally a Cox Proportional Hazards Model will be used to assess covariates influencing time to first exacerbation. Covariates will include treatment, gender, age, ATS stage, and smoking status. Time-to-first level II/level III exacerbation will be analyzed similarly. Health care resource utilization endpoints excluding work days lost will be analyzed using the time-to-event methodology described above for exacerbations. Additionally a Poisson regression model will be used to estimate the event rate per patient-month of follow-up for each endpoint separately.

Differences in pulmonary function at the end of the two week randomized Run-Out phase will be analyzed using the linear model described above. Effects will be included in the model for treatment and country. Least square means and associated 95% confidence intervals will be calculated on the change from baseline within each of the three groups and on the associated pre-specified treatment differences of interest.

Exacerbations with an onset during the Run-Out phase will be enumerated by treatment group [clinstat\091.pdf:2106-11].

III.C.10. DISPOSITION

Approximately 1259 patients were screened for the study. The number of patients who entered the single-blind period, were randomized to receive study medication, completed the study, were eligible for analyses, and who entered the open-label extension study are presented in the following table that shows about a 25% drop-out rate in all groups over this 6-month study [clinstat\091.pdf:74]:

NDA #21573 (12/24/02, N-000) STUDY 091: PATIENT DISPOSITION [clinstat\091.pdf:74, 236-7, 256]√			
	Treatment Group		
Disposition	Placebo n (% of randomized)	SB 207499 (15 mg bid) n (%of randomized)	Total n (%of randomized)
entered single-blind phase	--	--	973
randomized to 24-week DB phase	242 (100.0)	469 (100.0)	711 (100.0)
withdrawn from 24-week DB phase	63 (26.0)	121 (25.8)	184 (25.9)
ITT efficacy analysis	230 (95.0)	435 (92.8)	665 (93.5)
PP efficacy analysis	195 (80.6)	372 (79.3)	567 (79.7)
completed 24-week DB phase	179 (74.0)	348 (74.2)	527 (74.1)
DB = double-blind			

The disposition of patients entering the double-blind 2-week Run-Out period is shown in the following table [clinstat\091.pdf:75]:

NDA #21573 (12/24/02, N-000) STUDY 091: PATIENT DISPOSITION [clinstat\091.pdf:75, 253, 257]√			
	Treatment Sequence: 24-Week DB/Run-Out		
Disposition	P/P n (% of randomized)	SB/SB n (%of randomized)	SB/P n (%of randomized)
randomized to 2-week Run-Out	179 (100.0)	179 (100.0)	167 (100.0)
withdrawn from 2-week Run-Out	2 (1.1)	1 (0.6)	1 (0.6)
completed 2-week Run-Out	177 (98.9)	178 (99.4)	166 (99.4)
entered open label extension (040)	104 (58.1)	111 (62.0)	92 (55.1)
DB = double-blind P = placebo SB = SB-207499			

The table that follows includes all patient from the 24-week trial and the 2-week run-out period. In the latter case, placebo patients received placebo throughout both periods and SB 207499 patients received SB 207499 throughout both periods. Patients failing to complete the double-blind period were similarly frequent in the SB 207499 treatment group (26.0%) as in the placebo group (25.8%).

NDA #21573 (12/24/02, N-000) STUDY 091: REASON FOR EARLY TERMINATION BY TREATMENT GROUP [clinstat\091.pdf:77]√		
	Treatment	
Withdrawal Reason	Placebo (n = 242) n (%)	SB 207499 (n = 469) n (%)
adverse events*	32 (13.2)	78 (16.6)
COPD exacerbation	16 (6.6)	12 (2.6)
not due to a COPD exacerbation	16 (6.6)	66 (14.1)
protocol deviation, including non-compliance	11 (4.5)	18 (3.8)
lost to follow-up	9 (3.7)	10 (2.1)
insufficient therapeutic effect	1 (0.4)	2 (0.4)
other	10 (4.1)	13 (2.8)
total withdrawn prematurely	63 (26.0)	121 (25.8)
completed double-blind phase	179 (74.0)	348 (74.2)
* This row includes COPD exacerbations.		

The most frequent reason for early termination in both treatment groups was "adverse events" which were about 1.25 times more frequent in the SB 207499 group than in the placebo group. Thirty-two of 242 (13.2%) placebo patients and 78 of 469 (16.6%) patients in the SB 207499 group were withdrawn from double-blind treatment due to an adverse event. A very large portion of the SB 207499 group discontinued prematurely due to gastrointestinal complaints (10.9%) occurring during the double-blind period, compared with placebo (1.7%). There was a higher incidence of COPD exacerbations in the placebo group leading to withdrawal than in the SB 207499 group (6.6% and 2.6%, respectively) [clinstat\091.pdf:77, 161-7]. All percentages are based on the numbers of patients randomized to each treatment group. Similar findings occurred in studies 039 and 042.

III.C.11. DEMOGRAPHICS

Like most pharmaceutical studies, this was almost exclusively a trial conducted in Caucasians. Males were the disproportionately more frequent gender in both treatment groups. The dominant age range of patients enrolled in this COPD study was over 50, with a mean of 62.6 years. By inspection, the medians are very close to the means which suggests a fairly symmetrical distribution without much skewness. The frequencies of most characteristics were fairly evenly distributed between treatment groups. Other baseline demographic characteristics of interest are shown in the following table [clinstat\091.pdf:84, 88].

NDA #21573 (12/24/02, N-000) STUDY 091: DEMOGRAPHIC CHARACTERISTICS AT SCREENING (ALL RANDOMIZED PATIENTS) [clinstat\091.pdf:84, 88, 264, 268-9]√					
		Treatment Group			
		Placebo n = 242		SB 207499 15 mg bid n = 469	
Characteristic		n	(%)	n	(%)
Sex	Female	35	(14.5)	65	(13.9)
	Male	207	(85.5)	404	(86.1)
Race	Caucasian	237	(97.9)	461	(98.3)

NDA #21573 (12/24/02, N-000) STUDY 091: DEMOGRAPHIC CHARACTERISTICS AT SCREENING (ALL RANDOMIZED PATIENTS) [clinstat\091.pdf:84, 88, 264, 268-9]√					
		Treatment Group			
		Placebo n = 242		SB 207499 15 mg bid n = 469	
Characteristic		n	(%)	n	(%)
	Black	0		1	(0.2)
	Oriental	5	(2.1)	6	(1.3)
	Other*	0		1	(0.2)
Age, years	< 50	23	(9.5)	44	(9.4)
	50 - 65	111	(45.9)	218	(46.5)
	> 65	108	(44.6)	207	(44.1)
	Mean (SD)	62.6 (9.4)		62.9 (9.2)	
	Median	64		64	
	Min, Max	39, 84		39, 80	
Weight, kg.	Mean (SD)	71.8 (13.3)		74.6 (15.0)	
	Min, Max	42, 131		39, 130	
$FEV_{1.0}$ (L)	Mean (SD)	1.53 (0.46)		1.53 (0.48)	
	Min, Max	0.55, 3.46		0.57, 3.24	
Reversibility (%)	Mean (SD)	5.4 (8.8)		4.9 (8.2)	
	MIN, MAX	-21.6, 54.2		-37.4, 31.9	
* not further defined					

III.C.12. COMPLIANCE WITH TREATMENT

As stipulated in the protocol, patients were to be withdrawn from the study if study medication compliance at each visit during the double-blind period was not $\geq$ 80% and $\leq$ 120%. The following table shows that a greater percentage of placebo patients were compliant with their treatment than were SB 207499 patients, but compliance in both groups was over 90% [clinstat\091.pdf:97].

NDA #21573 (12/24/02, N-000) STUDY 091: PATIENT COMPLIANCE WITH TREATMENT DURING THE 24-WEEK DOUBLE-BLIND TREATMENT PERIOD [clinstat\091.pdf:97]√		
Compliance (%)	Treatment	
	Placebo (N = 242) n (%)	SB 207499 15 mg BID (N = 469) n (%)
< 80	9 (3.8)	31 (6.7)
80 - 120	231 (96.3)	431 (92.7)
> 120	0	3 (0.6)
mean (SD)	96.3 (7.8)	95.0 (12.2)
Min, Max	28.6, 107.1	14.3, 178.6
Compliance data were available for 224 patients in the placebo group and 471 patients in the SB 207499 group.		

III.C.13. CONCOMITANT COPD MEDICATION USE

The most frequently received medications were amoxycillin (9.1% and 7.7% of patients receiving placebo and SB 207499, respectively) and, in the placebo group,

methylprednisolone (5.8% of patients) and clavulanate (5.4% of patients) and, in the SB 207499 group, clavulanate (5.1% of patients). Of patients who required concomitant medications to treat exacerbations of COPD, a greater percent of placebo patients (55.7%) than SB 207499 patients (39.8%) used prednisolone, prednisone, methylprednisolone or deflazacort (systemic corticosteroids) [clinstat\091.pdf:96-7].

NDA #21573 (12/24/02, N-000) STUDY 091: NUMBERS OF PATIENTS (%) USING CONCOMITANT MEDICATIONS TO TREAT COPD EXACERBATIONS [clinstat\091.pdf:96]√

COPD Medication	Treatment	
	Placebo (N = 242) n (%)	SB 207499 15 mg BID (N = 469) n (%)
TOTAL*	79 (32.6)	108 (23.0)
amoxycillin	22 (9.1)	36 (7.7)
clavulanic acid	13 (5.4)	24 (5.1)
methylprednisolone	14 (5.8)	15 (3.2)
prednisone	13 (5.4)	15 (3.2)
ambroxol	1 (0.4)	10 (2.1)
prednisolone	11 (4.5)	8 (1.7)
acetycysteine	9 (3.7)	8 (1.7)
ceftriaxone	5 (2.1)	8 (1.7)
cefuroxime	6 (2.5)	7 (1.5)
paracetamol	9 (3.7)	5 (1.1)
deflazacort	6 (2.5)	5 (1.1)
ipratropium	6 (2.5)	5 (1.1)
doxycycline	5 (2.1)	5 (1.1)
salbutamol	9 (3.7)	4 (0.9)

* Total represents total number of patients receiving concomitant medication.

III.C.14. EFFICACY

III.C.14.a. PRIMARY MEASURES

The difference between treatments in the average change from baseline is shown in the following table. There was no mean change from baseline in the SB 207499 group and the placebo group showed a mean decrease of 30 ml. Hence, the mean difference in changes from baseline between groups was also 30 ml, which was not statistically significant.

NDA #21573 (12/24/02, N-000) STUDY 091: SUMMARY OF DIFFERENCE BETWEEN TREATMENTS IN AVERAGE CHANGE FROM BASELINE OVER 24 WEEKS (REPEATED MEASURES ANALYSIS) IN TROUGH $FEV_{1.0}$ (L) – ITT GROUP [clinstat\091.pdf:100, 411]√

Treatment Group	N	Change From Baseline				Comparison With Placebo			
		Mean*	SEM	Lower 95% CI	Upper 95% CI	Mean Diff.	Lower 95% CI	Upper 95% CI	Type I Error
placebo	230	-0.03	0.02	-0.06	0.01	--	--	--	--
SB 207499	435	0.00	0.02	-0.03	0.03	0.03	-0.00	0.06	0.055

* Mean values are adjusted for country and week.

The numbers of patient in the two treatment groups were fewer than the number who were randomized (placebo = 242, SB 207499 = 469). This means that either these patients failed to provide a baseline spirometry or dropped out before the first post-treatment spirometry was determined [7/9/03 Teleconference, 03-07-09_Tel.pdf].

The individual means in trough $FEV_{1.0}$ at each visit are shown in the table below from which the average change from baseline for the two treatments was calculated.

NDA #21573 (12/24/02, N-000) STUDY 091: MEAN TROUGH $FEV_{1.0}$ (L) IN THE ITT POPULATION BY VISIT AND TREATMENT GROUP [clinstat\091.pdf:102, 412]√

Week	Placebo		SB 207499	
	N	Mean* (SEM)	N	Mean* (SEM)
Baseline	232	1.45 (0.04)	443	1.46 (0.04)
2	229	1.41 (0.04)	431	1.45 (0.04)
4	223	1.43 (0.04)	417	1.45 (0.04)
8	213	1.42 (0.05)	393	1.48 (0.05)
12	203	1.41 (0.05)	375	1.46 (0.05)
16	196	1.41 (0.05)	367	1.47 (0.05)
20	190	1.38 (0.06)	355	1.47 (0.05)
24	179	1.40 (0.06)	344	1.45 (0.05)
Endpoint	232	1.39 (0.04)	443	1.43 (0.04)

* mean values were adjusted for country

The table shows a decline in mean trough $FEV_{1.0}$ in the placebo group that occurred over the first two weeks. The mean trough $FEV_{1.0}$ then varied slightly upwards and downwards over the remainder of the double-blind period. By comparison, the trough $FEV_{1.0}$ in the SB 207499 group never really changed from its baseline value. The entire non-significant difference between the two treatments was from the decline in the placebo group over the first two weeks of the double-blind period.

The SGRQ has a 100 point scale size (lower scores represent greater wellness), is divided into three domains and a minimum important difference of four units [www.atsqol.org most recent update April 2002]. The average change from baseline in total score of the SGRQ over 24 weeks of treatment is presented in the table that follows. This average was derived from testing done at baseline, Week 12 and Week 24.

NDA #21573 (12/24/02, N-000) STUDY 091: SUMMARY OF DIFFERENCE BETWEEN TREATMENTS IN AVERAGE CHANGE FROM BASELINE OVER 24 WEEKS (REPEATED MEASURES ANALYSIS) IN SGRQ TOTAL SCORE – ITT GROUP [clinstat\091.pdf:105, 427]√

Treatment Group	N	Change From Baseline				Comparison With Placebo			
		Mean*	SEM	Lower 95% CI	Upper 95% CI	Mean Diff.	Lower 95% CI	Upper 95% CI	Type I Error
placebo	197	-2.3	1.2	-4.6	0.0	--	--	--	--
SB 207499	369	-2.7	1.1	-4.8	-0.5	-0.4	-2.4	1.6	0.711

* Mean values were adjusted for country and week.

The numbers of patient in the two treatment groups were fewer than the numbers who were randomized. This means that either these patients failed to provide a baseline

SGRQ or dropped out before the first post-treatment SGRQ was determined [7/9/03 Teleconference, 03-07-09_Tel.pdf].

Both groups showed an average decrease (improvement) from baseline that was similar in the two treatment groups, with a very slight advantage for SB 207499. This mean change from baseline in both groups was less than the minimum important difference and a comparison of change from baseline between groups did not approach statistical significance. The mean SGRQ values for each treatment at each visit at which they were determined is shown in the following table.

NDA #21573 (12/24/02, N-000) STUDY 091: MEAN SGRQ (TOTAL SCORE) IN THE ITT POPULATION BY VISIT AND TREATMENT GROUP [clinstat\091.pdf:106, 428]√

Week	Placebo		SB 207499	
	N	Mean* (SEM)	N	Mean* (SEM)
Baseline	208	41.5 (1.6)	388	42.1 (1.4)
12	192	39.3 (1.7)	364	39.6 (1.6)
24	174	41.4 (2.2)	328	41.2 (2.1)
Endpoint	208	40.9 (1.8)	388	40.5 (1.6)

* mean values were adjusted for country

The mean SGRQ Total Score declined (improved) from baseline to Week 12 in the placebo group, finally increasing (worsening) at Week 24 to about the same level as it was at baseline. The SB 207499 group showed the same decline (improvement) at Week 12 followed by an increase (worsening) at Week 24 as did the placebo group but never returned completely to baseline.

The average change from baseline in score for the three sub-scales of the SGRQ over 24 weeks of treatment is presented in table below and shows only slight differences between the two treatments on all three sub-scales. SB 207499 is marginally better than placebo on the Symptoms and Activities sub-scales and the placebo is marginally better than SB 207499 on the Impacts sub-scale.

NDA #21573 (12/24/02, N-000) STUDY 091: SUB-SCALES OF SGRQ – CHANGES FROM BASELINE OVER 24 WEEKS IN SYMPTOMS, IMPACTS & ACTIVITIES SCORES OF THE SGRQ, ITT SAMPLE [clinstat\091.pdf:130, 508, 511, 514]√

Parameter Treatment Group	n	Change From Baseline			Comparison With Placebo		
		Mean* (SEM)	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI
SYMPTOMS SCORE							
placebo	201	-4.3 (2.0)	-8.2	-0.4	--	--	--
SB 207499**	375	-5.3 (1.8)	-9.0	-1.7	-1.1	-4.5	2.3
IMPACTS SCORE							
placebo	197	-2.2 (1.4)	-4.9	0.5	--	--	--
SB 207499**	369	-1.7 (1.3)	-4.2	0.8	0.5	-1.9	2.8
ACTIVITIES SCORE							
placebo	197	-1.0 (1.4)	-3.8	1.9	--	--	--
SB 207499**	369	-2.5 (1.4)	-5.1	0.2	-1.5	-4.0	1.0

* Mean values are adjusted for country. ** The dosage of SB 207499 is 15 mg. twice daily.

III.C.14.b. SECONDARY MEASURES

When averaged over 24 weeks, there was a 10 mL decrease from baseline in the mean clinic trough FVC in the SB 207499 group and a 20 mL decrease in the placebo group [clinstat\091.pdf:108, 110]. When averaged over 24 weeks, there was a decrease from baseline in the mean post-exercise breathlessness on the 11-point modified Borg Scale in the SB 207499 group (-0.16) and no change in the placebo group (0.00) [clinstat\091.pdf:112-3]. When change from baseline was averaged over 24 weeks, there was a greater decline (improvement) in the mean 11-point Summary Symptom Score (breathlessness (0-4 scale), cough and sputum production (each on a 0-3scale) in the SB 207499 group than in the placebo group (-0.36 and -0.25 points, respectively) [clinstat\091.pdf:115, 117]. When change from baseline was averaged over 24 weeks, there was an increase in the mean distance walked in both treatment groups, with a greater increase in the placebo group (7.3 m) than the SB 207499 group (5.1 m). This should be viewed in the context of the baseline walking distance of about 425 m for both groups [clinstat\091.pdf:119-20]. There was a difference in the exacerbation-free rates between the two treatment groups, with 63.9% and 51.1% of patients in the SB 207499 and placebo groups, respectively who were exacerbation-free at 24 weeks. Percent predicted $FEV_{1.0}$ was a risk factor for COPD exacerbations. The risk of COPD exacerbation increased by 20% for every 10% reduction in percent-predicted $FEV_{1.0}$. Gender showed an association with exacerbation-free survival. Males had a 34% lower risk than females. Patients not smoking had a 24% lower risk of exacerbations than those who smoked at baseline. Age was not associated with greater risk of exacerbations [clinstat\091.pdf:121-2].

III.C.14.c. TERTIARY MEASURES

The use of albuterol on an "as-needed" basis and the symptom-free days were analyzed as tertiary efficacy parameters and are presented here because they are usually-reviewed outcomes with some direct clinical relevance. At baseline the treatment groups had similar salbutamol usage, with a mean of 2.62 puffs/day in the placebo group and 2.73 puffs/day in the SB 207499 group. There were only small changes from baseline in salbutamol use over the study with a mean increase of 0.15 puffs/day in the placebo group and a mean decrease of 0.06 puffs/day in the SB 207499 group. Overall, patients treated with placebo had a mean of 1.8% of their days symptom free (i.e., free of cough, breathlessness and sputum) compared with a mean of 2.6% of days symptom-free for patients treated with SB 207499. This would amount a difference between groups of 1.3 symptom-free days over a 168-day, 24-week follow-up for both treatment groups [clinstat\091.pdf:130].

A first-dose effect was sought by measuring $FEV_{1.0}$ at baseline, 1, 2, 3, 4 hours after the first treatment and 30 minutes after receiving 400 mcg of albuterol. There was no response of SB 207499 or placebo to the treatment within the four hours post-dosing. Responsiveness, compared with baseline, to albuterol was minimally greater after SB 207499 (10.3% and 150 mL) than after placebo (8.3% and 120 mL) [clinstat\091.pdf:48,

125-6]. A last-dose effect was also sought by measuring the $FEV_{1.0}$ at baseline, before the last dose, 1, 2, 3, 4 hours post-dose and 30 minutes after receiving 400 mcg of albuterol. There was no difference between treatments in change in the $FEV_{1.0}$ in the four hours after the last dose. Albuterol responsiveness for the placebo group was slightly less (10.8% and 150 mL) than for the SB 207499 group (13% and 190 mL) [clinstat\091.pdf:48, 128, 416].

At the end of the 24-Week double-blind treatment period, patients entered a 2-week randomized, double-blind, Run-Out phase. Patients initially randomized to SB 207499 15mg twice daily were re-randomized to either SB 207499 15mg twice daily (treatment sequence S/S) or placebo (treatment sequence S/P). Patients initially randomized to placebo continued to take placebo during the Run-Out phase (treatment sequence P/P). Several comparative outcome variables were examined over the entire course of the study in patients newly assigned to these groupings at week 24. The utility of this grouping is hard to understand in a study that had failed to achieve statistical significance for either of its co-primary efficacy endpoints. However, the trough $FEV_{1.0}$ was selected from among them for display below [clinstat\091.pdf:132, 134, 425].

NDA #21573 (12/24/02, N-000) STUDY 091: MEAN TROUGH $FEV_{1.0}$ (L) IN THE ITT POPULATION BY VISIT AND TREATMENT GROUP ASSIGNED FOR THE RUN-OUT PHASE OF THE STUDY [clinstat\091.pdf:132-4, 425]√

	Placebo/Placebo		SB 207499/SB 207499		SB 207499/Placebo	
Week	N	Mean* (SEM)	N	Mean* (SEM)	N	Mean* (SEM)
Baseline	170	1.43 (0.06)	171	1.49 (0.06)	160	1.46 (0.06)
4	170	1.40 (0.06)	170	1.46 (0.06)	159	1.46 (0.06)
8	169	1.40 (0.06)	169	1.47 (0.06)	159	1.48 (0.06)
12	169	1.38 (0.06)	171	1.45 (0.06)	160	1.48 (0.06)
16	169	1.40 (0.06)	171	1.47 (0.06)	160	1.48 (0.06)
20	169	1.37 (0.06)	171	1.47 (0.06)	159	1.47 (0.06)
24	168	1.39 (0.06)	170	1.46 (0.06)	160	1.44 (0.06)
Run-Out	170	1.38 (0.06)	171	1.45 (0.06)	160	1.43 (0.06)

* Mean values are adjusted for country.

Differences between the mean trough $FEV_{1.0}$ at Week 24 and at Run-Out for each of the three assigned groups showed 10 ml declines for each of the three groups. It appears as if substituting placebo for SB 207499 at Run-Out was no different than continuing the SB 207499 and no different from continuing placebo treatment.

At Baseline and Week 24, spirograms were assessed before the first dose of double-blind study medication; 1, 2, 3, and 4 hours after the dose of double-blind study medication; and 30 ($\pm$ 5) minutes after administration of 4 puffs of albuterol (400 mcg via MDI with a spacer) [clinstat\091.pdf:125-6]. The results of the first dose over the first four hours show that the $FEV_{1.0}$ was unchanged in the placebo group and increased 10 mL in the SB 207499 group. Following albuterol administration, the $FEV_{1.0}$ increased from the pre-treatment (4-hour) value by 120 mL in the placebo group and by 140 mL in the SB 207499 group.

NDA #21573 (12/24/02, N-000) STUDY 091: MEAN CHANGE FROM BASELINE IN $FEV_{1.0}$ (L) AFTER THE FIRST DOSE OF DOUBLE-BLIND MEDICATION – ITT POPULATION [clinstat\091.pdf:126]				
Time	Placebo		SB 207499	
	n	Assessment Mean (SD)	n	Assessment Mean (SD)
baseline	240	1.45 (0.04)	463	1.46 (0.04)
1 hour	240	1.46 (0.04)	463	1.46 (0.04)
2 hours	239	1.46 (0.04)	462	1.46 (0.04)
3 hours	239	1.44 (0.04)	458	1.46 (0.04)
4 hours	236	1.45 (0.04)	456	1.47 (0.04)
30 min. after albuterol	237	1.57 (0.04)	460	1.61 (0.04)
Mean values are adjusted for country.				

Over the first four hours, after the last dose of study medication, the $FEV_{1.0}$ increased by 10 mL in the placebo group and increased by 20 mL in the SB 207499 group. Following albuterol administration, the $FEV_{1.0}$ increased from the pre-treatment (4-hour) value by 140 mL in the placebo group and by 170 mL in the SB 207499 group.

NDA #21573 (12/24/02, N-000) STUDY 091: MEAN CHANGE FROM BASELINE IN $FEV_{1.0}$ (L) AFTER THE LAST DOSE OF DOUBLE-BLIND MEDICATION – ITT POPULATION [clinstat\091.pdf:416]				
Time	Placebo		SB 207499	
	n	Assessment Mean (SD)	n	Assessment Mean (SD)
baseline	172	1.39	340	1.46
1 hour	171	1.40	337	1.48
2 hours	172	1.42	337	1.50
3 hours	171	1.40	334	1.49
4 hours	171	1.40	333	1.48
30 min. after albuterol	171	1.54	337	1.65
Mean values are adjusted for center.				

III.C.15. SAFETY

The safety data from this study will be included in the Integrated Summary of Safety.

III.D. PIVOTAL TRIAL CPMS-156

A Randomized, 24-week, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety and Tolerability of Ariflo (SB 207499, 15 mg BID) in Patients with Chronic Obstructive Pulmonary Disease (COPD)

III.D.1. LOCATIONS & DATES

This Phase 3 study was conducted at 132 centers in the United States and Canada. Patients were randomized in 126 of these centers. The first dose of single-blind medication was taken on 12 December 2000. The first and last doses of double-blind medication were administered on 11 January 2001 and 16 July 2002, respectively [clinstat\156.pdf:13].

III.D.2. SUMMARY

This was a Phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel-group study in patients with COPD, as defined by American Thoracic Society (ATS) guidelines. Patients had at least 11 visits over a 28-week period (Week –4, Screening, through Week 24). The study began with a 4-week, single-blind, placebo run-in period, after which eligible patients were randomized to receive either SB 207499 or matching placebo in a ratio of 1:1 for 24 weeks. One tablet of SB 207499 or matching placebo was taken twice daily, immediately after breakfast and after the evening meal. Albuterol MDI was used as rescue medication. This study was a duplicate of study 042 and 091 in all ways that reflected efficacy of the primary endpoint. Secondary-tertiary endpoints, even bearing the same names, were sometimes quite differently defined from the other three pivotal trials. Some were moved from self-assessed in patient diary entries to investigator-assessed at formal visits. Some were dropped and others added.

The primary efficacy endpoints were change from baseline in trough forced expiratory volume in one second ($FEV_{1.0}$) and change from baseline in total score of the St George's Respiratory Questionnaire (SGRQ). These were defined the same way as in the three other pivotal trials. The primary comparison was the average difference between the SB 207499 treatment group and the placebo treatment group over the 24 weeks of the double-blind period.

Patients failing to complete the double-blind period were more frequent in the SB 207499 treatment group (34.2%) than in the placebo group (23.6%). This was largely due to premature discontinuations because of adverse events (SB 207499 19.1%, placebo 10.3%) that were not due to COPD exacerbations (SB 207499 16.5%, placebo 8.1%). Withdrawals from the SB 207499 group were mostly due to gastrointestinal complaints occurring during the double-blind treatment period (SB 207499 12.4%, placebo 2.0%).

All percentages are based on the numbers of patients randomized to each treatment group. Compliance with the experimental treatment was 89.6% for patients assigned to the SB 207499 group and was 95.3% for patients assigned to placebo. Concomitant medications were used to treat COPD exacerbations in 22.6% of placebo patients and in 22.2% of SB 207499 patients. Prednisone was used to treat exacerbations in 37.0% of placebo patients and 39.8% of SB 207499 patients who required concomitant medication for a COPD exacerbation.

When averaged over 24 weeks of treatment and compared to baseline in a repeated measures analysis, there was 10 mL increase in the mean clinic trough $FEV_{1.0}$ in the SB 207499 group and a 20 mL decrease in the placebo group. The difference in mean changes from baseline between groups was statistically significant after adjustments for center and week. The mean trough $FEV_{1.0}$ in the placebo group decreased over the first month, remaining stable until a further decline occurred over the fifth and sixth months. By comparison, the trough $FEV_{1.0}$ in the SB 207499 group increased slightly from its baseline value over the first two weeks, remaining stable until the fifth and sixth months, when it first increased then decreased slightly. The SGRQ Total Score declined (improved) in both groups from baseline and the greater decline (improvement) occurred in the SB 207499 group. The decline in SGRQ Total Score did not achieve the minimal important difference of 4.0 for either group (SB 207499 -3.2, placebo -1.3). Neither did the difference between groups in mean change from baseline (difference 1.9). This is an example of an endpoint that is very likely to have been improved by the treatment and that the improvement is not likely to have made a difference to the patients, as a group. Miniscule mean changes in secondary and tertiary endpoints slightly favored SB 207499 over placebo.

III.D.3. OBJECTIVE

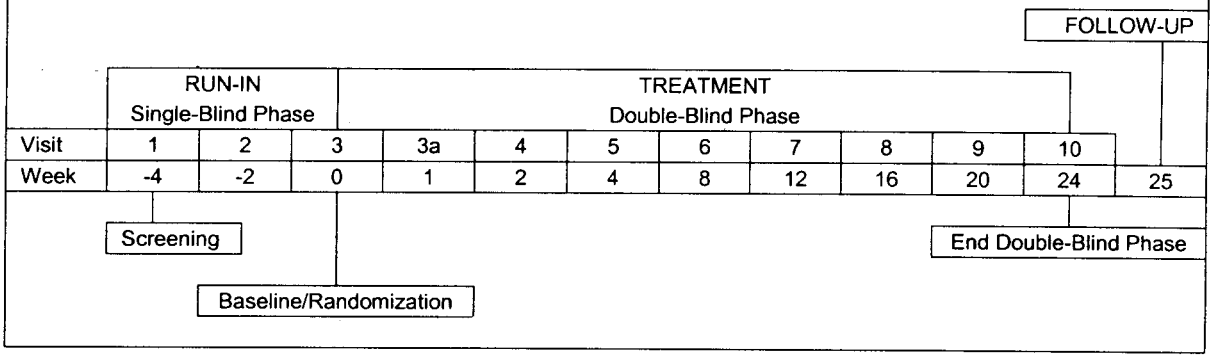
The primary objective was to demonstrate the clinical efficacy of oral SB 207499 (15 mg bid) versus placebo by assessment of trough forced expiratory volume in 1 second ($FEV_{1.0}$) and by total score of the St George's Respiratory Questionnaire over 24 weeks in patients with COPD [clinstat\156.pdf:13, 27, 1578].

III.D.4. DESIGN

The design of this protocol was identical to protocol 039 with a few exceptions. Randomization to SB 207499 or placebo was done on a 1:1 basis, as opposed to the 2:1 randomization done for the other three pivotal trials. Those patients who completed study 156 according to the protocol (i.e., through week 25), did not have the option of entering an open label long term extension (LTE) study [clinstat\156.pdf:28-32, 1579-82]. Several safety and efficacy variables were qualitatively recorded at formal visits, instead of daily. In some cases, the scoring was done by the investigator rather than the patient and in still other instances, new scoring systems were generated; e.g., "global assessments." See the VARIABLES section of this report for a detailed report of the

differences. Of the four pivotal trials, the design and procedures in this one were the most dissimilar to the others (039, 042, 091), though the two co-primary efficacy endpoints were identical.

NDA #21573 (12/24/02, N-000) STUDY 156: SCHEMATIC REPRESENTATION OF STUDY DESIGN [clinstat\156.pdf:29, 1581]√



III.D.5. PATIENTS

Up to 830 patients will be randomized to achieve 550 patients to satisfactorily complete the study. Approximately 140 centers in North America (United States and Canada) were expected to participate, with each center aiming to enroll between 6 and 24 patients. Patient inclusion, exclusion and randomization criteria for this trial were identical to the criteria for study 039. However, diary compliance and diary symptom-score criteria were not included in this protocol [clinstat\156.pdf:32-4, 1584-6, 1595-6].

III.D.6. TREATMENT

The treatment was the same as in study 039, with the exception of the batch numbers of the active treatment and the placebo.

NDA #21573 (12/24/02, N-000) STUDY 156: APPEARANCE, FORMULATION AND BATCH NUMBERS OF STUDY MEDICATION [clinstat\156.pdf:4, 34]√

Study Drug	Appearance	Formulation	Dose	Batch Number
SB 207499	off-white, round, convex	tablet	15 mg	U98258
placebo	off-white, round, convex	tablet	--	U99060
Appendix A contains the Certificate of Analysis [clinstat\156.pdff:2565-7].				

Prior, treatment, rescue, allowed and prohibited medications for this study (156) were the same as for study 039 [clinstat\156.pdf:37, 1639-42].

III.D.7. VARIABLES

The variables that were measured are the same in this trial (156) as they were in protocol 039 with some exceptions. In this trial the diary card was used only to record

adverse events, "The diary will provide space for the patient to record if they feel differently since starting the study medication" [clinstat\156/pdf:1631]. Albuterol and concomitant medication use and COPD symptom scores were not assessed by diary card entries. Instead, these were moved to the study visits and executed as responses to general questions. Albuterol rescue medication use was tracked by qualitative questions at study visits. During Visits 2 - 10, the Investigator was required to record the patient's daily albuterol use via MDI according to the following [clinstat\156.pdf:1622]:

Much less than usual
Less than usual
About the same as usual
More than usual
Much more than usual

COPD Symptom Score was moved from the daily diary to a question-answer scale filled out at each visit. Though it bears the same title as in the three other pivotal trials, this is an entirely different scale with different numbers of scale divisions and different definitions for them [clinstat\156.pdf:51]:

NDA #21573 (12/24/02, N-000) STUDY 156: COUGH AND SPUTUM ASSESSMENTS [clinstat\156.pdf:50-1]	
COUGH - "How troubled have you been by cough today?"	
0	No symptoms at all
1	Some symptoms, but hardly noticeable
2	Symptoms noticeable and a little uncomfortable
3	Symptoms definitely noticeable and uncomfortable
4	Symptoms very bad and extremely uncomfortable
SPUTUM PRODUCTION - "How much sputum have you produced today?"	
0	No sputum at all
1	Some sputum, but not as much as usual
2	As much as usual
3	More than usual
4	A lot more than usual

Investigator and patient global assessments were completed at Week 24 and early withdrawal visits. Patients were asked, "How do you feel now in comparison with when you started to take study medication"? Investigators were asked, "How do you assess the patient's COPD now in comparison to when they started to take study medication"? Both the patient and Investigator responded according to the following [clinstat\156.pdf:51]:

Very much improved
Much improved
Minimally improved
No change
Minimally worse
Much worse
Very much worse

At Baseline and Week 24 (Visits 3 and 10), PFTs were first assessed prior to administration of albuterol (180mcg via MDI with a spacer), 30 (± 5) minutes after albuterol administration, and 1, 2, 3, and 4 hours after the dose of double-blind study medication [clinstat\156.pdf:48].

The Holter monitoring and diary card review were absent from the flow chart. The first was not included in this protocol, but diary card review was included in descriptions of individual study methodologies and procedures [clinstat\156.pdf:1594]. Concomitant medication use was determined in response to questioning at study visits [clinstat\156.pdf:1642, 1776]. An additional evaluation at Early Withdrawal was added for "post-exercise SaO_2 and breathlessness" and "exercise tolerance (6-minute walk)" [clinstat\156.pdf:1583, 039.pdf:1982-3].

Patients were instructed to call the Investigator to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhea, or vomiting) which caused them concern or interfered with their daily activities (including eating and sleeping). These were termed "GI AEs of concern." The Investigator completed a clinical assessment of the gastrointestinal adverse event(s) within 24 hours of occurrence. The patient had a fecal occult blood test kit available at home to obtain a fecal sample prior to reporting to the clinic for evaluation of a gastrointestinal AE of concern. When the patient reported a GIAE of concern, the Investigator instructed the patient to use the FOB test kit dispensed for this purpose. The patient was scheduled for a clinic visit within 24 hours and instructed to return the FOB test. The assessment at the clinic included a structured history of the adverse event including relationship to the time of dosing with study medication and food intake; a physical examination with emphasis on the abdomen; an assessment of orthostatic changes in heart rate and blood pressure; and a review of the fecal occult blood test results. In addition, laboratory assessments were performed: complete blood count with white cell differential; amylase, electrolytes, blood glucose, and liver function tests; urinalysis including microscopic examination, if indicated; and a fecal occult blood test.

When the fecal occult blood test samples were analyzed, the Investigator questioned the patient to determine if the results may have been affected by menstruation, bleeding hemorrhoids, blood in the urine, medications, vitamins, or foods. Whenever the patient could not provide a fecal sample prior to or at the clinic visit, the Investigator obtained a sample by digital rectal exam. Patients were provided with replacement fecal occult blood test kits whenever the blank kits were used. This was the standard methodology for handling GI AEs of concern for all of the pivotal controlled and the two long-term uncontrolled trial.

In this protocol and for the first time in the development of this drug, if the fecal occult blood test was positive or if the patient reported melena during the randomized treatment phase of the study, referral to a gastroenterologist was mandatory for a complete colonoscopy as soon as possible within 10 to 14 days of the clinic visit. The colonoscopy was said to have emphasized visualization of the transverse colon with reporting of positive or negative findings, irrespective of other identified pathology or causes for gastrointestinal bleeding [clinstat\156.pdf:54].

III.D.8. PROCEDURE FLOW CHART

NDA #21573 (12/24/02, N-000) STUDY 156: PROCEDURE FLOW CHART [CLINSTAT\156.PDF:1583]													
	Screen		Base-line								End DB	Early W/D[1]	Safety F/U
Visit	**1**	**2**	**3**	**3a**	**4**	**5**	**6**	**7**	**8**	**9**	**10**		
Week	**-4**	**-2**	**0**	**+1**	**+2**	**+4**	**+8**	**+12**	**+16**	**+20**	**+24**		**+25**
medical & surgical history	X												
PA chest radiograph[4]	X												
DLCO[6]	X												
pulmonary history & symptoms	X												
medication history	X												
St. George's Respiratory Questionnaire (SGRQ)			X					X			X	X	
SF-36			X								X	X	
study medication compliance		X	X	X	X	X	X	X	X	X	X	X	
concomitant medications/procedures		X	X	X	X	X	X	X	X	X	X	X	X
baseline signs, symptoms & adverse events		X	X	X	X	X	X	X	X	X	X	X	X
exacerbation assessment/resource use	X	X	X	X	X	X	X	X	X	X	X	X	X
overall breathlessness (modified Borg Scale)	X	X	X		X	X	X	X	X	X	X		
physical examination (PE)[2]	X		X								X	X	X[3]
vital signs (BP, HR)	X[5]	X	X[5]	X	X	X	X	X	X	X	X[5]	X[5]	X
resting 12-lead electrocardiogram (ECG)	X		X	X	X	X	X	X	X	X	X	X	X[6]
exercise tolerance (6-minute walk)	X	X	X			X	X	X	X	X	X	X	
post-exercise SaO_2 & breathlessness	X	X	X			X	X	X	X	X	X	X	
albuterol reversibility [9]	X												
pulmonary functions (PFTs) without albuterol[10]		X	X		X	X	X	X	X	X	X	X	X
hourly PFTs for 4 hours post first & last dose[14]			X								X		
laboratory tests	X		X[8]	X	X	X	X	X	X[9]	X[9]	X[8]	X[8]	X[3, 9]
pharmacokinetic evaluations (PK)[12]			X			X		X			X		
arterial blood gas (ABG) & SaO_2 [13]			X								X		

1. Patients who stop taking study medication between clinic visits will attend the clinic within 24 hours for an early withdrawal visit.
2. To include a respiratory examination.
3. If abnormalities at previous visit for patients who complete Visit 10 or withdraw from the study.
4. Postero-anterior chest X-ray must be performed at Visit 1 unless the film from a chest X-ray within the 12 weeks prior to Visit 1 is available to the Investigator.
5. Including Orthostatic vital signs.

6. DLCO should be done between Visit 1 and Visit 3 if not performed during the previous 24 weeks or if the results are unavailable.
7. Before and 15 to 30 (±5) minutes after administration of 180 mcg albuterol via a MDI with a spacer to determine % predicted FEV1, FVC, FEF25-75, PEFR, and FEV1: FVC.
8. In addition to usual laboratory tests, three fecal occult blood tests will be performed between Visits 1 and 3, between Visits 9 and 10, and at early withdrawal; amylase will be measured at Visit 3.
9. Urinary beta-HCG tests will be performed in females of childbearing potential. No other laboratory samples will be collected at Visits 8 and 9.
10. Includes FEV1, FVC, FEF25-75, PEFR, and FEV1:FVC measured by centralized spirometry by the same person at each visit.
11. A diary will be used to record if patients feel different since starting study medication.
12. Visit 3: 3 hours post-dose. Visit 5: trough and 0.5-3 hours post-dose. Visit 7: trough and 3-10 hours post-dose. Visit 10: trough only.
13. In patients with <40% of predicted FEV1 at Visit 1 and resting SaO2 <88% or if the patient lives at a high altitude.
14. Pulmonary function tests 30 (±5) minutes after albuterol followed by 4-hour post-double-blind drug assessments at Visits 3 and 10.

III.D.9. STATISTICS

Originally, a sample size of 740 patients was planned, yet in order to obtain 550 completed patients, the total number of patients planned for randomization was increased to 830. Patients were randomized in a 1:1 ratio of SB 207499 to placebo. Approximately 140 centers in North America (United States and Canada) were expected to participate, with each center aiming to enroll between 4 and 24 patients. Assuming a standard deviation in $FEV_{1.0}$ change from baseline at any given visit of 210 mL, a correlation between visits of 0.68, and a significance level of 0.05, the indicated sample size will have greater than 90% power to detect a clinically meaningful difference of 50 mL in $FEV_{1.0}$. A difference of 50 mL was chosen based on retrospective analysis of data from Study 039. The sample size will also have more than 90% of power to detect a 4 unit difference (assuming a standard deviation of 12) in SGRQ at significance level of 0.05 [clinstat\156.pdf:59-60].

The primary conclusion of the study was based on a repeated-measures model on the change from baseline in the primary endpoints. Effects for treatment, time and center were included in the model. Inference was based on the average treatment effect over all protocol-defined double-blind visits. Follow-up and unscheduled visits for early withdrawal or other reasons were not included in the repeated measures analysis. Time was treated as a nominal variable. An unstructured correlation matrix was used and estimated using restricted maximum likelihood (REML). The difference between treatment groups was evaluated through a t-test on the least-square means. Ninety-five percent (95%) confidence intervals were calculated on the least-square means of the two groups and on their difference. The default (model-based) estimator was used to estimate the standard errors of the fixed effects.

In the pre-NDA meeting with FDA, GSK was requested to change the covariance structure from compound symmetry to unstructured to be consistent with the previous three pivotal studies. For some variables, the pre-defined model (with center and treatment as factors) did not converge in using SAS procedure Proc Mixed. In these cases, center was removed from the model. For the primary endpoints, the homogeneity of treatment effect with respect to week and center was assessed through addition of treatment-by-week interaction and treatment-by center interaction terms to the final model described above. Interaction terms were tested at a significance level of 0.10. Consistency of the treatment effect over visits was further examined through graphical methods. As a treatment-by-time interaction in $FEV_{1.0}$ was observed, a repeated measures model as described above was performed using only the data from Weeks 16 to 24 of the double-blind period.

The effects of age, sex, % predicted $FEV_{1.0}$ and baseline smoking status on response were also explored. All four covariates were added to the final model described above. Although the estimation of treatment effect is usually robust with respect to the

choice of covariance structure, and the unstructured covariance model generally provides reasonable assumptions about the relationship in longitudinal data, other structures were also explored. Likelihood ratio tests were performed to evaluate the degree to which information was lost by moving away from the unstructured covariance matrix. To further examine the normality assumption, normal probability plots of the marginal residuals were examined. The residuals were output from the final model described above.

Sporadically missing data from patients completing the study was assumed to be missing at random (MAR). For patients who discontinued the study, MAR was not assumed. Patients were classified as withdrawals or completers and a nominal variable reflecting this categorization was defined in the mixed model and assessed for significance. No further formal exploration of the MAR assumption was carried out. To further describe the impact of dropouts, descriptive analyses were provided for the subgroup of patients who completed the study. An additional analysis was performed in which the worst (lowest) $FEV_{1.0}$ and worst (highest) SGRQ values were imputed for withdrawn patients at visits subsequent to their withdrawal. In addition, a pattern mixture model was used to assess the impact of missing data.

In addition to the repeated measures analysis described above an analysis of variance (ANOVA) model was performed at each protocol-defined double-blind visit as well as at endpoint. Endpoint was defined as the last on-therapy observation for each patient during the double-blind period. The ANOVA model included effects for treatment and center. Least squares means and associated 95% confidence intervals were calculated for each treatment group. Ninety-five percent (95%) confidence intervals were also calculated on the difference in the least-square means.

Subgroup analyses were performed to describe the response in the populations described below. Descriptive statistics (mean, median, standard deviation, minimum and maximum) of the baseline, endpoint and change from baseline to endpoint were provided for each of the subgroups. No inferential analyses were performed. The analysis of continuous secondary and tertiary endpoints was performed using the repeated measures methodology described above. An ANOVA model as described above was also performed at each protocol-defined visit and endpoint.

Differences in the distribution of time-to-first COPD exacerbation were tested using the log-rank test. The exacerbation-free survival rate at 24 weeks along with 95% confidence intervals was estimated for each treatment group using the Kaplan-Meier product limit method. Patients with no exacerbations were censored at the date of their last dose of randomized study medication.

To assess the impact of age, sex, baseline smoking status and % predicted $FEV_{1.0}$ on time-to-first COPD exacerbation, a Cox Proportional Hazards model was used. The relative risk (for SB 207499 versus placebo) of a COPD exacerbation and associated 95%

confidence interval were estimated after adjusting for the effects of these covariates. To take account of the recurring nature of COPD exacerbations, a marginal proportional hazards model proposed by Wei, Lin and Weissfeld was also performed. The first two exacerbations for each patient were used for the analysis. This analysis proceeds by analyzing the first and second exacerbations separately, estimating the variance-covariance matrix of the parameter estimates, and performing simultaneous inference. A weighted estimate of the relative risk along with 95% confidence intervals is then estimated.

The analysis of healthcare utilization data was performed in a similar way to the analysis of COPD exacerbations. For each type of utilization (hospitalization, physician/ emergency room [ER] visit or intensive care unit [ICU] stay), Kaplan-Meier estimates and log rank test as described above were performed. An analysis which looks at any utilization, regardless of type, was also performed. Additionally, a Poisson regression model was used to estimate an annualized rate of utilization along with 95% confidence intervals for each treatment group. This analysis was done for each utilization type and across utilization types.

The intent-to-treat (ITT) population included all patients who received randomized study medication and had a baseline efficacy evaluation and at least one on-therapy efficacy evaluation during the double-blind period. Data collected more than one day after the last dose of study medication were excluded from the analysis. All efficacy analyses, with the exception of COPD exacerbations, were performed for the ITT population, the primary population in this study. COPD exacerbations were analyzed for randomized patients [clinstat\156.pdf:63-6].

III.D.10. DISPOSITION

Approximately 1252 patients were screened for the study. The number of patients who entered the single-blind period, were randomized to receive study medication, completed the study, were eligible for analyses, and who entered the open-label extension study are presented in the following table that shows about a 29% drop-out rate in the total group over this 6-month study. There were about 50% more dropouts in the SB 207499 group than the placebo group [clinstat\156.pdf:67, 221-2, 242].

NDA #21573 (12/24/02, N-000) STUDY 156: PATIENT DISPOSITION [clinstat\156.pdf:67, 221]√			
	Treatment Group		
Disposition	Placebo n (% of randomized)	SB 207499 (15 mg bid) n (%of randomized)	Total n (%of randomized)
entered single-blind phase	--	--	1252
randomized to 24-week DB phase	407 (100.0)	418 (100.0)	825 (100.0)
withdrawn from 24-week DB phase	96 (23.6)	143 (34.2)	239 (29.0)
ITT efficacy analysis	377 (92.6)	364 (87.1)	741 (89.8)
PP efficacy analysis	363 (89.2)	353 (84.4)	716 (86.8)
completed 24-week DB phase	311 (76.4)	275 (65.8)	586 (71.0)

NDA #21573 (12/24/02, N-000) STUDY 156: PATIENT DISPOSITION [clinstat\156.pdf:67, 221]√			
	Treatment Group		
Disposition	Placebo n (% of randomized)	SB 207499 (15 mg bid) n (%of randomized)	Total n (%of randomized)
DB = double-blind			

In the table that follows, patients failing to complete the double-blind period were more frequent in the SB 207499 treatment group (34.2%) than in the placebo group (23.6%).

NDA #21573 (12/24/02, N-000) STUDY 156: REASON FOR EARLY TERMINATION BY TREATMENT GROUP [clinstat\156.pdf:69, 242]√		
	Treatment	
Withdrawal Reason	Placebo (n = 407) n (%)	SB 207499 (n = 418) n (%)
adverse events*	42 (10.3)	80 (19.1)
COPD exacerbation	9 (2.2)	11 (2.6)
not due to a COPD exacerbation	33(8.1)	69 (16.5)
protocol deviation, including non-compliance	10 (2.5)	6 (1.4)
lost to follow-up	5 (1.2)	7 (1.7)
insufficient therapeutic effect	6 (1.5)	8 (1.9)
other**	33 (8.1)	42 (10.0)
total withdrawn prematurely	96 (23.6)	143 (34.2)
completed double-blind phase	311 (76.4)	275 (65.8)
* This row includes COPD exacerbations. ** The most common reason for "other" was withdrawn consent.		

The most frequent reason for early termination in both treatment groups was "adverse events" which were about twice as frequent in the SB 207499 group as in the placebo group. Adverse events that were not due to an exacerbation of COPD were twice as frequent in the SB 207499 group. A very large portion of the SB 207499 group discontinued prematurely due to gastrointestinal complaints (12.4%) occurring during the double-blind period, compared with placebo (2.0%). There was a slightly lower incidence of COPD exacerbations in the placebo group leading to withdrawal than in the SB 207499 group (2.2% and 2.6%, respectively) [clinstat\156.pdf:69, 139-144]. All percentages are based on the numbers of patients randomized to each treatment group. Similar findings occurred in studies 039 and 042.

III.D.11. DEMOGRAPHICS

Like most pharmaceutical studies, this was almost exclusively a trial conducted in Caucasians. Males were the disproportionately more frequent gender in both treatment groups. The dominant age range of patients enrolled in this COPD study was over 50, with a mean of 62.6 years. By inspection, the medians are very close to the means which suggests a fairly symmetrical distribution without much skewness. The frequencies of most characteristics were fairly evenly distributed between treatment groups. Other baseline demographic characteristics of interest are shown in the following table [clinstat\156.pdf:].

NDA #21573 (12/24/02, N-000) STUDY 156: DEMOGRAPHIC CHARACTERISTICS AT SCREENING (ALL RANDOMIZED PATIENTS) [clinstat\156.pdf:75, 77, 251, 256-7]√					
		Treatment Group			
		Placebo n = 407		SB 207499 15 mg bid n = 418	
Characteristic		n	(%)	n	(%)
Sex	Female	156	(38.1)	183	(43.8)
	Male	251	(61.7)	235	(56.2)
Race	Caucasian	377	(92.6)	392	(93.8)
	Black	25	(6.1)	25	(6.0)
	Oriental	1	(0.2)	0	
	Other*	4	(1.0)	1	(0.2)
Age, years	< 50	25	(6.1)	17	(4.1)
	50 - 65	184	(45.2)	201	(48.1)
	> 65	198	(48.6)	200	(47.8)
	Mean (SD)	64.4 (8.7)		64.5 (8.2)	
	Median	65.0		65.0	
	Min, Max	41, 80		41, 80	
Weight, kg.	Mean (SD)	77.6 (18.6)		76.8 (18.0)	
	Min, Max	34, 167		35, 144	
$FEV_{1.0}$ (L)	Mean (SD)	1.45 (0.53)		1.40 (0.48)	
	Min, Max	0.48, 3.18		0.50, 2.98	
Reversibility (%)	Mean (SD)	8.6 (6.4)		8.6 (6.4)	
	MIN, MAX	0.0, 34.7		0.0, 31.3	
* not further defined					

III.D.12. COMPLIANCE

As stipulated in the protocol, patients were to be withdrawn from the study if study medication compliance at 2 consecutive visits during the double-blind period was <80% or >120%. The following table presents overall compliance for all randomized patients [clinstat\156.pdf:84-5]:

NDA #21573 (12/24/02, N-000) STUDY 156: COMPLIANCE WITH TREATMENT MEDICATION ESTABLISHED BY PILL COUNTS, ALL RANDOMIZED PATIENTS [clinstat\156.pdf:85, 370-13]√		
	Treatment	
Compliance % of number of patients evaluated	Placebo (N = 407) n (%)	SB 207499 (N = 418) n (%)
< 80	19 (4.7)	41 (10.0)
80 – 120	382 (95.3)	369 (89.6)
> 120	0	2 (0.5)
N	401	412
Mean Percent (SD)	95.34 (9.38)	93.60 (24.50)
Min, Max Percent	30.00, 114.29	3.85, 500.00

Medication compliance was worse for the SB 207499 treatment group than for the placebo group with twice as many patients demonstrating less than 80% compliance in the SB 207499 group (10.0%) as the placebo group (4.7%).

III.D.13. CONCOMITANT COPD MEDICATION USE

The percentage of patients receiving medication for COPD exacerbation was similar in both groups (22.6% placebo vs. 22.2% SB 207499). The most frequently administered medications were prednisone, salbutamol, and azithromycin. Oral corticosteroid use was similar in both treatment groups (SB 207499 39.8%, placebo 37.0%) expressed as a percent of patients receiving concomitant medication for a COPD exacerbation [clinstat\156.pdf:84].

NDA #21573 (12/24/02, N-000) STUDY 156: NUMBERS OF PATIENTS (%) USING CONCOMITANT MEDICATIONS TO TREAT COPD EXACERBATIONS [clinstat\156.pdf:84]√

COPD Medication	Treatment Group	
	Placebo (N = 407) n (%)	SB 207499 15 mg BID (N = 418) n (%)
TOTAL*	92 (22.6)	93 (22.2)
prednisone	34 (8.4)	37 (8.9)
salbutamol	35 (8.6)	34 (8.1)
azithromycin	22 (5.4)	22 (5.3)
levofloxacin	14 (3.4)	15 (3.6)
amoxicillin trihydrate	3 (0.7)	9 (2.2)
guafenesin	11 (2.7)	8 (1.9)
ipratropium bromide	8 (2.0)	7 (1.7)
clarithromycin	8 (2.0)	4 (1.0)

* Total represents total number of patients receiving medication for COPD exacerbations.

III.D.14. EFFICACY

III.D.14.a. PRIMARY MEASURES

The difference between treatments in the average change from baseline is shown in the following table. The numbers of patient in the two treatment groups were fewer than the number who were randomized (placebo = 407, SB 207499 = 418). This means that either these patients failed to provide a baseline spirometry or dropped out before the first post-treatment spirometry was determined [7/9/03 Teleconference, 03-07-09_Tel.pdf]. There was a mean increase from baseline of about 10 mL in the SB 207499 group and a mean decrease from baseline of about 20 mL in the placebo group. The difference in mean changes from baseline between groups was 20 mL, which was statistically significant. This somewhat counter-intuitive math probably results from adjustments for center and week as well as round-off errors when these quantities are displayed in units of Liters.

NDA #21573 (12/24/02, N-000) STUDY 156: SUMMARY OF DIFFERENCE BETWEEN TREATMENTS IN AVERAGE CHANGE FROM BASELINE OVER 24 WEEKS (REPEATED MEASURES ANALYSIS) IN TROUGH $FEV_{1.0}$ (L) – ITT GROUP [clinstat\156.pdf:86, 387]√									
		Change From Baseline				Comparison With Placebo			
Treatment Group	N	Mean*	SEM	Lower 95% CI	Upper 95% CI	Mean Diff.	Lower 95% CI	Upper 95% CI	Type I Error
placebo	377	-0.02	0.01	-0.03	-0.00	--	--	--	--
SB 207499	364	0.01	0.01	-0.01	0.02	0.02	0.00	0.04	0.024
* Mean values are adjusted for center and week.									

The individual means in trough $FEV_{1.0}$ at each visit are shown in the table below from which the average change from baseline for the two treatments was calculated.

NDA #21573 (12/24/02, N-000) STUDY 156: MEAN TROUGH $FEV_{1.0}$ (L) IN THE ITT POPULATION BY VISIT AND TREATMENT GROUP [clinstat\156.pdf:87, 2702]√				
	Placebo		SB 207499	
Week	N	Mean* (SEM)	N	Mean* (SEM)
Baseline	383	1.39 (0.03)	377	1.35 (0.03)
2	373	1.38 (0.03)	361	1.37 (0.03)
4	365	1.37 (0.03)	338	1.37 (0.03)
8	351	1.37 (0.03)	319	1.37 (0.03)
12	332	1.37 (0.03)	302	1.37 (0.03)
16	317	1.37 (0.03)	292	1.39 (0.03)
20	315	1.36 (0.03)	278	1.38 (0.04)
24	311	1.35 (0.03)	273	1.37 (0.04)
Endpoint	383	1.35 (0.03)	377	1.35 (0.03)
* Mean values were adjusted for center.				

The table shows the mean trough $FEV_{1.0}$ in the placebo group decreased over the first month, remaining stable until a further decline occurred over the fifth and sixth months. By comparison, the trough $FEV_{1.0}$ in the SB 207499 group increased slightly from its baseline value over the first two weeks, remaining stable until the fifth and sixth months, when it first increased then decreased slightly. The significant difference between the two treatments was mostly from the decline in the placebo group over the 24 weeks of follow-up and less so from an increase in the SB 207499 group.

The SGRQ has a 100 point scale size (lower scores represent greater wellness), is divided into three domains and a minimum important difference of four units [www.atsqol.org most recent update April 2002]. The average change from baseline in total score of the SGRQ over 24 weeks of treatment is presented in the table that follows. This average was derived from testing done at baseline, Week 12 and Week 24.

The mean change from baseline in the SGRQ Total Score is shown in the table that follows, along with the difference in mean change from baseline between the two treatment groups. The SGRQ Total Score declined (improved) in both groups from baseline and the greater decline (improvement) occurred in the SB 207499 group. The decline in SGRQ Total Score did not achieve the minimal important difference for either group (SB 207499 -3.2, placebo -1.3). Neither did the difference between groups in

mean change from baseline (difference 1.9). This is an example of an endpoint that is very likely to have been improved by the treatment and that the improvement is not likely to have made a difference to the group of patients.

NDA #21573 (12/24/02, N-000) STUDY 156: SUMMARY OF DIFFERENCE BETWEEN TREATMENTS IN AVERAGE CHANGE FROM BASELINE OVER 24 WEEKS (REPEATED MEASURES ANALYSIS) IN SGRQ TOTAL SCORE – ITT GROUP [clinstat\156.pdf:90, 411]√

Treatment Group	N	Change From Baseline				Comparison With Placebo			
		Mean*	SEM	Lower 95% CI	Upper 95% CI	Mean Diff.	Lower 95% CI	Upper 95% CI	Type I Error
placebo	337	-1.3	0.6	-2.5	-0.1	--	--	--	--
SB 207499	304	-3.2	0.6	-4.5	-2.0	-1.9	-3.5	-0.3	0.017

* Mean values were adjusted for country and week.

The mean SGRQ Total Score values for each treatment at each visit at which they were determined is shown in the following table. The mean SGRQ Total Score declined (improved) from baseline to Week 12 in the both groups, decreasing (improving) further at Week 24 in both treatment groups. The decline from baseline to Week 24 was about the same for each group.

NDA #21573 (12/24/02, N-000) STUDY 156: MEAN SGRQ (TOTAL SCORE) IN THE ITT POPULATION BY VISIT AND TREATMENT GROUP [clinstat\156.pdf:91, 412]√

Week	Placebo		SB 207499	
	N	Mean* (SEM)	N	Mean* (SEM)
Baseline	369	43.5 (0.9)	359	43.8 (0.9)
12	335	42.0 (1.0)	294	41.5 (1.1)
24	304	40.7 (1.1)	264	40.6 (1.2)
Endpoint	369	42.6 (1.0)	359	41.4 (1.0)

* mean values were adjusted for center

The average change from baseline in score for the three sub-scales of the SGRQ over 24 weeks of treatment is presented in table below and shows only slight differences between the two treatments on all three sub-scales. SB 207499 declines (improves) more from baseline than placebo, but both treatments were associated with improving scores on all three sub-scales.

NDA #21573 (12/24/02, N-000) STUDY 156: SUB-SCALES OF SGRQ – CHANGES FROM BASELINE OVER 24 WEEKS IN SYMPTOMS, IMPACTS & ACTIVITIES SCORES OF THE SGRQ, ITT SAMPLE [clinstat\156.pdf:106-7, 479, 482, 485]√

Parameter Treatment Group	n	Change From Baseline			Comparison With Placebo		
		Mean* (SEM)	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI
SYMPTOMS SCORE							
placebo	339	-2.3 (1.1)	-4.4	-0.2	--	--	--
SB 207499**	308	-4.4 (1.1)	-6.6	-2.1	-2.0	-4.8	0.7
IMPACTS SCORE							
placebo	337	-1.4 (0.6)	-2.7	-0.2	--	--	--
SB 207499**	304	-2.7 (0.7)	-4.0	-1.4	-1.3	-3.1	0.5
ACTIVITIES SCORE							
placebo	337	-1.2 (0.7)	-2.5	0.1	--	--	--

NDA #21573 (12/24/02, N-000) STUDY 156: SUB-SCALES OF SGRQ – CHANGES FROM BASELINE OVER 24 WEEKS IN SYMPTOMS, IMPACTS & ACTIVITIES SCORES OF THE SGRQ, ITT SAMPLE [clinstat\156.pdf:106-7, 479, 482, 485]√							
Parameter		Change From Baseline			Comparison With Placebo		
Treatment Group	n	Mean* (SEM)	Lower 95% CI	Upper 95% CI	Mean Difference	Lower 95% CI	Upper 95% CI
SB 207499**	304	-3.7 (0.7)	-5.1	-2.4	-2.6	-4.5	-0.7
* Mean values are adjusted for center.			** The dosage of SB 207499 is 15 mg. twice daily.				

III.D.14.b. SECONDARY MEASURES

When averaged over 24 weeks, there was no change from baseline in the mean clinic trough FVC in the SB 207499 group and a 20 mL decrease in the placebo group [clinstat\156.pdf:93, 95]. When averaged over 24 weeks, there was a decrease from baseline in the mean post-exercise breathlessness on the 11-point modified Borg Scale in the SB 207499 group (-0.10) and a small increase in the placebo group (0.05) [clinstat\156.pdf:97-8]. There was a difference in the exacerbation-free survival rates between the two treatment groups, with 66.7% and 67.4% of patients in the SB 207499 and placebo groups, respectively who were exacerbation-free at 24 weeks. Baseline smoking status, age and percent predicted $FEV_{1.0}$ were not a risk factor for COPD exacerbations. Gender showed an association with exacerbation-free survival with a relative risk of 1.47 in females compared to males [clinstat\156.pdf:100]. Exacerbation Level 2 (additional treatment from outpatient physician encounter) or 3 (hospital admission) free survival at 24 weeks was 79.5% for the placebo group and 75.6% for the SB 207499 group [clinstat\156:pdf:100-1, 1645].

III.D.14.c. TERTIARY MEASURES

The use of rescue medicine (albuterol) on an "as-needed" basis was analyzed as a tertiary efficacy parameter and is presented here because it is usually-reviewed outcome with some direct clinical relevance. In this protocol, symptom-free days was omitted because it was not a defined endpoint. Rescue medicine use was defined by recall on a 5-point ordinal scale of use compared to "usual" use and recorded at each visit. Baseline was the Visit 3 (Week 0) frequency distribution among the five categories comparing the two treatment groups. Endpoint was defined as the last on-therapy observation for each patient during the double-blind period and was also expressed as a frequency distribution among the five categories. The table below shows these five categories collapsed into three, less than usual, about the same as usual and more than usual use at baseline and at endpoint. A greater percent of patients in the placebo group used "more than usual" rescue medication at endpoint than at baseline. By comparison, a lesser percent of patients in the SB 207499 group used "more than usual" rescue medication at endpoint than at baseline. One wonders if the definition of "usual" was the same one used by each patient at baseline and at endpoint.

NDA #21573 (12/24/02, N-000) STUDY 156: NUMBER (%) OF PATIENTS CATEGORIZED BY RESCUE MEDICINE USE AT BASELINE AND AT ENDPOINT [clinstat\156.pdf:512]				
Time Point & Treatment	N	Rescue Medicine (albuterol) Use Compared To "Usual"		
		Less Than Usual	About The Same	More Than Usual
PLACEBO				
Baseline	387	82 (21.2)	249 (64.3)	56 (14.5)
Endpoint	387	84 (21.7)	215 (55.6)	88 (22.7)
Difference in %	--	0.5	-8.7	8.2
SB 207499				
Baseline	389	78 (20.1)	235 (60.4)	76 (19.5)
Endpoint	389	90 (23.1)	234 (60.2)	65 (16.7)
Difference in %	--	3.0	-0.2	-2.8

Another tertiary measure that will be included in this section is the 6-minute walk test. This endpoint was designated as a secondary endpoint in the other three pivotal efficacy trials (039, 042, 091) but designated as tertiary in this protocol. There was a small increase in the 6-minute walking distance that favored SB 207499 over placebo in this study [clinstat\156.pdf:112, 440]. The difference between treatments in mean changes from baseline is less than 1.5% of either baseline.

NDA #21573 (12/24/02, N-000) STUDY 156: CHANGES FROM BASELINE OVER 24 WEEKS IN DISTANCE WALKED AVERAGED OVER 24 WEEKS, ITT POPULATION [clinstat\156.pdf:112, 440]√					
Treatment	n	Approximate Baseline	Change From Baseline		Difference
			Mean Change	SEM	
Placebo	356	369.8	2.8	3.6	
SB 207499	330	364.7	7.9	3.7	5.0
Mean values adjusted for week.					

A first-dose effect was sought by measuring $FEV_{1.0}$ at baseline and 30 minutes after receiving 180 mcg of albuterol. Then a dose of experimental treatment was administered and the $FEV_{1.0}$ was determined 1, 2, 3 and 4 hours after the first experimental treatment. There was no difference in response to albuterol between the SB 207499 and placebo treatments. Within the four hours after the experimental treatment there was also no difference between treatment groups in the mean $FEV_{1.0}$ [clinstat\0156.pdf:390]. A last-dose effect was also sought by measuring the $FEV_{1.0}$ at baseline before the last dose and 30 minutes after receiving 180 mcg of albuterol. Then the experimental treatment was administered and the $FEV_{1.0}$ was determined 1, 2, 3 and 4 hours post-dose. There was no difference between treatments at any of the $FEV_{1.0}$ measurement periods [clinstat\156.pdf:392].

III.D.15. SAFETY

The safety data from this study will be included in the Integrated Summary of Safety.

III.E. DOSE-FINDING TRIAL CPMS-032

A 6 Week Multicentre, Double-Blind, Placebo-Controlled, Parallel-Group Study To Determine The Safety, Tolerability And Efficacy Of Oral SB 207499 (Ariflo 5, 10 and 15 mg Twice Daily) As Therapy In Out-Patients With Chronic Obstructive Pulmonary Disease (COPD)

III.E.1. LOCATIONS & DATES

This study was carried out in sixty centres in Austria, France, Germany, the Netherlands and the UK. The first and last doses of double-blind medication were taken on 21 March 1997 and the 6 January 1998, respectively [clinstat\032.pdf:3].

III.E.2. SUMMARY

Over 400 patients were randomized into four groups, placebo and three doses of SB 207499 (5, 10 & 15 mg twice daily) for a six-week, parallel-group, dose-finding Phase 2 study in COPD patients. Over all weeks, patients who received placebo showed small declines in trough $FEV_{1.0}$ and patients randomized to various doses of SB 207499 showed small increases. There was no dose-ordering among the active treatments. At the end of the study, the sixth week, the change in trough $FEV_{1.0}$ from baseline comparing each treatment to placebo showed statistical significance of the 15 mg twice daily dose and a maximum change from baseline of 130 mL. Pharmacokinetic sampling and results will be dealt with in a separate review by the Clinical Pharmacology And BioPharmaceutics reviewer.

III.E.3. OBJECTIVES

The primary objective was to compare the efficacy of oral SB 207499 (5, 10 and 15mg twice daily) with placebo when administered for 6 weeks to patients with COPD in terms of improvement in trough forced expiratory volume in one second ($FEV_{1.0}$). Secondary objectives were: (i) to evaluate the dose response of SB 207499, (ii) to compare the safety and tolerability of oral SB 207499 (5, 10 and 15mg twice daily) versus placebo when administered for 6 weeks to patients with COPD and (iii) to obtain plasma levels of SB 207499 and to investigate any relationship between plasma levels of SB 207499 and clinical effect [clinstat\032.pdf:3].

III.E.4. DESIGN

This was a multi-center, Phase 2, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study comparing 3 doses of SB 207499 (5, 10, 15mg twice daily) and placebo in patients with COPD. Patients received placebo twice daily during a

2-week single-blind run-in period. Eligible patients then received 6 weeks of randomized double-blind treatment followed by 1 week of follow-up [clinstat\032.pdf:3, 24].

III.E.5. PATIENTS

Patients aged 40-80 years with a clinical diagnosis of COPD (European Respiratory Society definition), a cigarette smoking history of $\geq$ 10 pack years, a pre-bronchodilator $FEV_{1.0}/FVC$ ratio $\leq$ 70%, post-bronchodilator $FEV_{1.0}$ 30-70% of that predicted for age, sex and height, post-bronchodilator reversibility of < 15% and/or < 200mL, dyspnea during daily activities and SaO2 of $\geq$ 90% were eligible for the study. Patient target sample size was 350 to provide 260 evaluable [clinstat\032.pdf:3].

III.E.6. TREATMENT

SB 207499 was initially provided as capsules, then as tablets following a change of formulation, containing 5 or 10mg of SB 207499 with matching placebo capsules/tablets. Two capsules/tablets were taken in the morning and two in the evening, after food. Batch numbers: SB 207499 capsules: U96190 (5mg), U95254 (10mg); placebo capsules: U96098; SB 207499 tablets: U97091 (5mg), U97092 (10mg); placebo tablets: U97090 [clinstat\032.pdf:4].

III.E.7. VARIABLES

Efficacy Parameters: the primary efficacy variable was the difference between placebo and treatments in mean change from baseline of the trough $FEV_{1.0}$ at week 6 (visit 7). Type I Error correction was by the modified Bonferroni procedure of Hochberg. Secondary efficacy variables were other tests of pulmonary function (FVC, PEFR, FEF25-75, FEF75), first dose effects on pulmonary function tests, exercise tolerance test, use of beta-2 agonists, dyspnea during usual daily activities and after exercise, other symptoms of COPD, SaO2 at rest, COPD exacerbation and Quality of Life assessments (St. George's Hospital Respiratory Questionnaire (SGRQ) and SF-36). Safety Parameters: safety was assessed by recording adverse experiences (AEs), laboratory data, vital signs and ECGs. Blood samples were collected pre-dose at Visits 4, 5, 6 and 7 (Weeks 1, 2, 4 and 6) and post-dose at Visit 7 (between 0.5-3 or 3-8 hours) for measurement of SB-207499 plasma concentrations by liquid chromatography with tandem mass spectrometry. Concentration-relationships were explored for selected efficacy endpoints and AEs [clinstat\032.pdf:4, 1298].

III.E.8. STATISTICS

Analysis of variance was used to test for the effects of treatment, country and treatment-by-country interaction. Least squares means with associated 95% confidence intervals (CIs) were calculated for each treatment group. Pairwise comparisons were made between each active dose and placebo by using t-tests on the least squares means

and 95% CIs were calculated on the treatment difference. The significance level was adjusted using the modified Bonferroni procedure of Hochberg. Repeated measures analysis was performed on the change from baseline. Fisher's exact test was used to assess differences between each of the active dose groups and placebo for the number of patients with a reduction in beta-2 agonist use [clinstat\032.pdf:4].

III.E.9. DISPOSITION

The disposition of patients by treatment group is shown in the table that follows form the modified ITT population. Over all groups, 16% of the randomized patients failed to complete the six-week trial.

NDA #21573 (12/24/02, N-000) STUDY 032: NUMBERS OF PATIENTS AND DISPOSITION [clinstat\032.pdf:5, 58]

Disposition	Placebo	SB 207499 Twice Daily			Totals
		5 mg	10 mg	15 mg	
screened	--	--	--	--	604
randomized	106	109	102	107	424
completed	89	92	85	89	355
modified-ITT population	106	109	102	107	424
safety population*	105	108	100	105	418
PP population**	90	94	79	87	350
total withdrawn	17	17	17	18	69

* 6 patients (center 121) excluded from the safety assessment due to incorrect allocation of study medication
** number of patients in Per Protocol population for the primary efficacy outcome

III.E.10. DEMOGRAPHICS

In general, there were no marked differences between the groups in demographic characteristics, although there was a slightly higher proportion of female patients in the SB 207499 15 mg twice daily group than in the other groups. Predominantly, this was a study of male Caucasians.

NDA #21573 (12/24/02, N-000) STUDY 032: BASELINE DEMOGRAPHIC CHARACTERISTICS OF THE MODIFIED ITT POPULATION [clinstat\032.pdf:5, 62, 157]

Characteristic		Placebo	SB 207499 Twice Daily		
			5 mg	10 mg	15 mg
Sex (n, %)	Male	83 (78.3)	89 (81.7)	84 (82.4)	80 (74.8)
	Female	23 (21.7)	20 (18.3)	18 (17.6)	27 (25.2)
Age (years)	mean (SD)	63.2 (8.7)	63.6 (9.3)	62.3 (9.3)	62.0 (10.5)
Race (n, %)	white	106 (100)	109 (100)	99 (97.1)	105 (98.1)
	black	0	0	1 (1.0)	2 (1.9)
	oriental	0	0	1 (1.0)	0
	other	0	0	1 (1.0)	0
pre-bronchodilator FEV_{10} (L)	mean (SD)	1.42 (0.49)	1.38 (0.43)	1.46 (0.48)	1.43 (0.46)
salbutamol reversibility (%)	mean (SD)	4.3 (8.3)	6.2 (7.8)	6.3 (8.2)	4.8 (9.0)

III.E.11. EFFICACY

The primary endpoint was comparison between each experimental treatment group and placebo at week 6 with the study-wide Type I Error corrected by the modified Bonferroni procedure of Hochberg at that visit. Only the 15 mg treatment group was statistically separable from placebo by this measure.

NDA #21573 (12/24/02, N-000) STUDY 032: TROUGH $FEV_{1.0}$ AT EACH VISIT IN ABSOLUTE UNITS OR AS CHANGE FROM BASELINE (L) [clinstat\032.pdf:75]

Visit	Placebo		5 mg		10 mg		15 mg	
	n	Mean or Change from Mean	n	Mean or Change from Mean	n	Mean or Change from Mean	n	Mean or Change from Mean
Baseline*	106	1.37	109	1.31	102	1.37	107	1.32
Week 1	105	-0.02	105	0.04	98	0.03	105	0.06
Week 2	100	-0.02	99	0.07	89	0.02	98	0.09
Week 4	95	-0.01	96	0.06	87	0.02	95	0.09
Week 6	91	-0.03	95	0.02	85	-0.01	90	0.13
Endpoint	105	-0.02	105	0.04	98	-0.00	105	0.12

* in absolute units

Examination of the entire table reveals that the placebo patients generally showed a reduction in trough $FEV_{1.0}$ from baseline over all visits. All active treatment groups generally showed an increase by the same measure. There was no dose-ordering of this effect. Over all visits, patients receiving the 5 mg dose showed greater improvements over baseline than did those receiving the 10 mg dose. Patients who received the 15 mg dose showed the greatest mean change of $FEV_{1.0}$ over baseline of up to 130 mL.

III.E.12. SAFETY

The safety data from this study will be included in the Integrated Summary of Safety.

III.F. DOSE-FINDING TRIAL CPMS-038

A Multicenter, Double-Blind, Placebo-Controlled, Parallel-Group Study To Evaluate The Safety, Tolerability, And Efficacy Of Oral SB 207499 (2.5 and 5 mg Twice Daily) For Four Weeks In Out-Patients With Chronic Obstructive Pulmonary Disease (COPD)

III.F.1. LOCATIONS & DATES

This was a multicenter study of 46 centers in the United States. It began on the March 27, 1997 and ended on August 16, 1997 [clinstat\038.pdf:3].

III.F.2. SUMMARY

Over 200 patients were randomized into three groups, placebo and two doses of SB 207499 (2.5 & 5.0 mg twice daily) for a four-week, parallel-group, dose-finding Phase 2 study in COPD patients. Over all weeks, patients who received placebo showed small declines in trough $FEV_{1.0}$ and patients randomized to various doses of SB 207499 showed small changes, both increases and decreases from baseline. At the end of the study, the fourth week, the change in trough $FEV_{1.0}$ from baseline, comparing each treatment to placebo, did not show statistical significance of either dose of SB 207499. Pharmacokinetic sampling and results will be dealt with in a separate review by the Clinical Pharmacology And BioPharmaceutics reviewer.

III.F.3. OBJECTIVES

The primary objective was to evaluate the effects of oral SB 207499 on forced expiratory volume in one second ($FEV_{1.0}$) in out-patients with COPD. Secondary objectives were determining clinical safety and tolerability [clinstat\038.pdf:3, 16].

III.F.4. DESIGN

This was a phase II, randomized, double-blind, placebo-controlled, parallel group, dose-ranging study. The study population consisted of patients who had a diagnosis of COPD. COPD was defined in this study according to American Thoracic Society guidelines by a pre-bronchodilator $FEV_{1.0}$/FVC (forced vital capacity) ratio of less than 0.7, post-bronchodilator $FEV_{1.0}$ 30-70 % predicted for age, gender and height, and post-bronchodilator reversibility of less than 15%. In addition, patients were required to have a minimum 10 pack year cigarette smoking history to be eligible to participate in the study.

Each patient participated for approximately seven weeks. Patients who satisfied the entry criteria at screening Visit 1 were enrolled in the study, and commenced a 2-

week single-blind run-in period during which they received oral SB 207499-matched placebo capsules twice daily. All medication for COPD, except inhaled short-acting beta-2 agonists and anticholinergic agents, were discontinued prior to Visit 1 according a pre-defined schedule. Patients must not have been taking oral or inhaled corticosteroids for at least 4 weeks prior to Visit 1.

Patients who met the randomization and compliance criteria at the end of the 2 week single-blind run-in period were randomly assigned to one of three study medication treatment arms at Baseline (Visit 3). The treatment arms comprised of either 2.5 mg SB 207499, 5 mg SB 207499 or SB 207499-matched placebo capsules twice daily, administered in a double-blind manner for a period of four weeks [clinstat\038.pdf:17].

III.F.5. PATIENTS

Patients aged 40-80 years with a clinical diagnosis of COPD (European Respiratory Society definition), a cigarette smoking history of $\geq$ 10 pack years, a pre-bronchodilator $FEV_{1.0}$/FVC ratio $\leq$ 70%, post-bronchodilator $FEV_{1.0}$ 30-70% of that predicted for age, sex and height, post-bronchodilator reversibility of < 15%, dyspnea during daily activities and SaO2 of $\geq$ 90% were eligible for the study. Patient target sample size was 350 to provide 260 evaluable. In order to obtain 80% power with a significance level of 5% after adjusting for multiple comparisons, 60 patients were required per treatment arm [clinstat\038.pdf:21, 46].

III.F.6. TREATMENT

SB 207499 was provided as a size 2, white, opaque, hard gelatin capsule containing 2.5 mg (batch U96191), or 5 mg (batch U96231) of SB 207499. Matching placebo capsules (batch U96098) were also provided for the single-blind phase of the study and for the placebo arm of the double-blind phase of the study. Medications were to be kept in locked storage areas with limited access and dispensed according to the protocol. These medications were stored under controlled room temperatures of 59-86° F (15-30° C) [clinstat\038.pdf:23].

III.F.7. VARIABLES

The primary efficacy endpoint was the change from baseline of the clinic trough $FEV_{1.0}$ comparing each active treatment to placebo. Secondary endpoint variables were additional spirographic measures, 6-minute walk, dyspnea assessment (modified Borg scale), COPD symptoms, rest and exercise transcutaneous SaO_2, arterial blood gases, use of rescue albuterol, SF-36 and exacerbation rates. PK samples will be obtained during this trial. Safety data will include ECG, vital signs, clinical laboratory and adverse events [clinstat\038.pdf:34-5,49, 859].

III.F.8. STATISTICS

The primary efficacy variable, $FEV_{1.0}$, was analyzed as change from baseline at the end of treatment (week 4, visit 6). Analysis of variance was used to identify the effect of treatment, center, and treatment-by-center interaction using PROC GLM of the Statistical Analysis System (SAS) for these analyses. If a significant interaction was detected at 0.1 level of significance, further analyses were performed to ascertain the nature of the interaction. If interaction effect was not significant, a reduced model with effects due to treatment and center was used to report differences between the treatment groups.

Dose response was assessed by linear regression for the primary efficacy variable. A statistically significant slope resulted in pairwise comparisons with no adjustment. If the slope was not statistically significant, pairwise comparisons were made of each active dose level of SB 207499 against placebo with adjustment for multiple comparisons using the modified Bonferroni procedure. An endpoint analysis of the change from baseline in FEV1 was also performed to assess the effect of patient dropouts prior to completion of double-blind treatment. Here endpoint was defined as the last efficacy evaluation during the treatment phase [clinstat\038.pdf:859-60].

III.F.9. DISPOSITION

The disposition of patients by treatment group is shown in the table that follows form the modified ITT population. Over all groups, 7.6% of the randomized patients failed to complete the four-week trial.

NDA #21573 (12/24/02, N-000) STUDY 038: NUMBERS OF PATIENTS AND DISPOSITION [clinstat\038.pdf:51]√				
Disposition	Placebo	SB 207499 Twice Daily		Totals
		2.5 mg	5 mg	
screened	--	--	--	379
entered SB phase	--	--	--	269
randomized*	75	72	77	224
completed study	69	67	71	207
modified-ITT population	75	72	77	224
total withdrawn	6	5	6	17
* These patients constitute the safety population.				

III.F.10. DEMOGRAPHICS

In general, there were no marked differences between the groups in demographic characteristics, although there was a slightly higher proportion of female patients in the SB 207499 2.5 mg twice daily group than in the other groups. Predominantly, this was a study of Caucasians.

NDA #21573 (12/24/02, N-000) STUDY 038: BASELINE DEMOGRAPHIC CHARACTERISTICS OF THE MODIFIED ITT POPULATION [clinstat\038.pdf:57, 123]				
Characteristic		Placebo	SB 207499 Twice Daily	
			2.5 mg	5 mg
Sex (n, %)	Male	42 (56)	36 (50)	45 (58.4)
	Female	33 (44)	36 (50)	32 (41.6)
Age (years)	mean (SD)	65.4 (9.0)	64.0 (10.0)	63.8 (8.3)
Race (n, %)	white	72 (96.0)	70 (97.2)	72 (93.5)
	black	1 (1.3)	1 (1.4)	3 (3.9)
	oriental	0	1 (1.4)	0
	other	2 (2.7)	0	2 (2.6)
pre-bronchodilator $FEV_{1.0}$ (L)	mean (SD)	1.39 (0.46)	1.30 (0.46)	1.41 (0.49)
salbutamol reversibility (%)	mean (SD)	5.28 (11.05)	7.15 (6.94)	5.01 (6.67)

III.F.11. EFFICACY

The primary endpoint was comparison between each experimental treatment group and placebo at week 4 with the study-wide Type I Error corrected by the modified Bonferroni procedure of Hochberg at that visit. Over all weeks, patients who received placebo showed small declines in trough $FEV_{1.0}$. Patients randomized to the two doses of SB 207499 showed small changes, both increases and decreases from baseline. At the end of the study, the fourth week, the change in trough $FEV_{1.0}$ from baseline, comparing each treatment to placebo, did not show statistical significance of either dose of SB 207499.

NDA #21573 (12/24/02, N-000) STUDY 038: TROUGH $FEV_{1.0}$ AT EACH VISIT IN ABSOLUTE UNITS OR AS CHANGE FROM BASELINE (L) [clinstat\038.pdf:68-9]						
Visit	Placebo		2.5 mg		5 mg	
	n	Mean or Change from Mean	n	Mean or Change from Mean	n	Mean or Change from Mean
Baseline*	75	1.33	72	1.28	77	1.37
Week 1	70	-0.00	71	0.03	75	0.02
Week 2	70	-0.03	70	--0.02	73	0.00
Week 4	70	-0.03	70	0.00	73	-0.02
Endpoint	70	-0.03	71.	-0.00	75	-0.02
* in absolute units						

III.F.12. SAFETY

The safety data from this study will be included in the Integrated Summary of Safety.

III.G. HPA AXIS SUPPRESSION TRIAL CPMS-147

A Randomized, Double-Blind Placebo-Controlled, Two-Period Crossover Study to Investigate the Effects of SB-207499 on the Hypothalamo-Pituitary-Adrenal (HPA) Axis in Healthy Volunteers.

III.G.1. LOCATIONS & DATES

The study was conducted at a single center in the United Kingdoms.. The first and last doses of double-blind medication were taken on 27 March 2000 and 8 June 2000, respectively [clinstat\147.pdf:9].

III.G.2. SUMMARY

This was a randomized, double-blind, placebo-controlled, two-period, cross-over study that randomized 20 healthy volunteers (10 male, 10 female) between the ages 18 and 55 to investigate the effect of SB-207499 on plasma prolactin, adrenal corticotropic hormone (ACTH) and serum/urinary cortisol levels, in healthy volunteers. The study was conducted over two sessions with repeat oral dosing, separated by a washout period of 14-34 days. Each session consisted of 7 days of twice daily dosing with 15 mg SB-207499 twice daily or matched placebo. In each session, prolactin, ACTH and cortisol were monitored over the 24 hour period prior to dosing on day -1 and for 24 hours after dosing on Day 7. Urinary cortisol over these 24 hour periods was also measured, together with creatinine to calculate cortisol/creatinine ratio.

Twenty subjects were recruited of whom 19 subjects received both regimens, SB-207499 15 mg twice daily and matching placebo. Mean serum levels of prolactin over 24 hours on days -1 and 7 were presented separately for males and females for each treatment group. Males on both days for both treatments had very similar mean prolactin levels (about 200 miu/L) that showed little fluctuation throughout the day. In females, the mean prolactin level was lowest at 10:00 am (about 200 miu/L), rising to a peak at the end of the day at midnight (about 300 miu/L). This pattern was apparently independent of the treatment and day of analysis, -1 or 7. Serum cortisol in both genders and regardless of treatment or day of analysis showed a zenith (200-400 nmol/L) at 10:00 am and a nadir at 10:00 pm to midnight (75-100 nmol/L). ACTH showed changes similar in direction and timing to cortisol but with much more subdued excursions (range or means over 24 hours 10-30 pg/mL). Once again, there were no differences in serum ACTH with regard to gender, treatment or day of analysis. Urinary cortisols collected over 24 hours for both days of analysis in males showed no treatment effect.

None of these variables showed any difference between genders and treatments over time. However, this was a very small study carried out for a very short time. The apparent reassurance that these results offer must be considered with appreciation for the

limited ability of even a very large number of patients to demonstrate a systemic effect of physiological consequence; e.g., growth suppression in children with inhaled and nasal corticosteroids in the absence of a signal from any conventionally accepted tests of HPA axis suppression.

An additional concern is that adrenal hypertrophy was shown in two species (monkey and rat) and a no observed adverse event level (NOAEL) for this end-organ toxicity was never identified for either. For both animal models, the lowest dose tested showed the toxic effect: monkeys at 1 mg/kg and rats at 5/mg/kg.

III.G.3. OBJECTIVES

The primary objective was to investigate the effect of SB-207499 on plasma prolactin levels in healthy volunteers. The secondary objective was to investigate the effect of SB-207499 on adrenal corticotropic hormone (ACTH) and serum/urinary cortisol in healthy volunteers [clinstat:147.pdf:9, 20].

III.G.4. DESIGN

This study was conducted in a randomized, double blind, placebo-controlled, two-period crossover design to investigate the effect of SB-207499 (15 mg twice daily for 7 days) on the HPA axis in healthy male and female volunteers. The study was conducted over two sessions with repeat oral dosing, separated by a washout period of 14-34 days. Each session consisted of 7 days of twice daily dosing with 15 mg SB-207499 twice daily or matched placebo. In each session, prolactin, ACTH and cortisol were monitored over the 24 hour period prior to dosing on day 1 and for 24 hours after dosing on Day 7. Samples were taken at the following time points:

NDA #21573 (12/24/02, N-000) STUDY 147: SAMPLING TIMES FOR SERUM PROLACTIN, ACTH & CORTISOL ON THE DAY -1 AND DAY 7 [clinstat\147.pdf:21]							
Target Time (hours military)	**1000**	**1200**	**1500**	**1800**	**2200**	**0000**	**1000**
Day -1 (hours pre-dose)	-24	-22	-19	-16	-12	-10	0
Day 7 (hours post-dose)	0	2	5	8	12	14	24

Urinary cortisol over these 24 hour periods was also measured, together with creatinine to calculate cortisol/creatinine ratio.

Volunteers were also instructed to follow the restrictions noted below. They were to refrain from caffeine containing drinks (i.e. coffee, tea, and cola, chocolate) for 48 hours prior to each visit to the Unit, including screening and follow-up and while staying in the Unit. They were not to have more than 4 cups of caffeinated drinks on all of the other dosing days. They were to refrain from strenuous physical exercise/exertion for 48 hours prior to each visit to the Unit including screening and follow-up and while within the Unit. They were to refrain from consuming alcoholic drinks for 48 hours prior to each visit to the Unit including screening and follow-up and while within the Unit. Also,

they were to refrain from drinking more than 3 units of alcohol (male) or 2 units of alcohol (female), on other days when taking a dose of study medication. 1 unit is equivalent to half a pint of beer or 1 measure of spirits or 1 glass of wine. They were to refrain from consuming liquorice for 48 hours prior to each visit to the Unit, including screening and follow-up and while within the Unit. They were to fast from midnight on evenings prior to visiting the Unit and to refrain from taking morning study medication at home before all morning visits to the Unit [clinstat\147.pdf:9-10, 21, 27].

III.G.5. SUBJECTS

Twenty subjects (10 males and 10 females) were recruited in order to get evaluable data for a minimum of 8 males and 8 females. In- and exclusion criteria are listed below [clinstat\147.pdf:23-5, 34].

III.G.5.a. INCLUSION CRITERIA

1. Non-smoking male or female aged between 18 and 55 years inclusive.
2. A negative pre-study Hepatitis B surface antigen and negative Hepatitis C result within 3 months of the start of the study.
3. Male volunteers who are not attempting to father a child during and up to 3 months after the study. Female volunteers who are not attempting to become pregnant during and up to 3 months after the study.
4. Females require a negative pregnancy test at the pre-study medical examination and at each of the 2 sessions.
5. A female who has experienced regular menstrual cycles of between 26 and 30 days for at least 2 months prior to entering the study and is not using an oral contraceptive pill (OCP) or a hormone coated intrauterine device (IUD). Women using a double-barrier method of contraception (for example spermicide and condoms or IUD which is not hormone coated).
6. Or a female who has been sterilized and is not receiving hormone replacement therapy (HRT).
7. Or a female who is post-menopausal, defined as not having menstruated in the last 2 years.
8. Body weight above 50 kg but within 25% of ideal weight for sex, height, frame and age.
9. No abnormality on clinical examination. A volunteer with a clinical abnormality may be included only if the Principal Investigator considers that the abnormality will not introduce additional risk factors and will not interfere with the study procedure.
10. No previous medical or family history of endocrine disorders/diseases.
11. No abnormality on clinical chemistry or hematology examination at the pre-study medical. Volunteers with laboratory parameters outside the reference range for this

age group will only be included if the Principal Investigator considers that such findings will not introduce additional risk factors.

12. A negative pre-study urine drug screen.
13. A 12-lead electrocardiogram (ECG) at the pre-study medical which is normal.
14. Subjects with prolactin, ACTH, serum/urinary cortisol and thyroid stimulating hormone (TSH) levels within the normal reference range at screening. Subjects who do not fall within the normal reference ranges may be included within the study if in the opinion of the Principal Investigator this will not compromise the subject or affect the outcome of the study.

III.G.5.b. EXCLUSION CRITERIA

1. Women experiencing menopausal symptoms.
2. Women on an oral contraceptive pills (OCP), hormone replacement therapy (HRT) or using a hormone coated intrauterine device (IUD).
3. The volunteer has received prescribed medication within 14 days prior to the first dosing day, which in the opinion of the Principal Investigator will interfere with the study procedures or compromise safety.
4. The volunteer has received over-the-counter (OTC) medicine within 48 hours prior to the first study day. Subjects who have taken OTC medication may still be entered into the study, if, in the opinion of the Principal Investigator, the medication received will not interfere with the study procedures or compromise safety.
5. Abuse of alcohol defined as an average weekly intake of greater than 21 units or an average daily intake of greater than 3 units in male subjects, or an average weekly intake of greater than 14 units or an average daily intake of greater than 2 units in female subjects. One (1) unit is equivalent to a half-pint of beer or 1 measure of spirits or 1 glass of wine.
6. Exposure to more than 3 new chemical entities within 12 months prior to the first dosing day.
7. Participation in a trial with a new chemical entity within the last 112 days.
8. Participation in a trial with any drug within 84 days before the start of the study.
9. Blood donation >750 mL within the previous 6 weeks (males), blood donation >500 mL within the previous 4 weeks (males) or 6 weeks (females) or if participation in the study will result in the volunteer having donated more than 1500 mL blood (males) or 1000 mL (females) (including this study) in the previous 12 months.
10. History or presence of gastrointestinal, hepatic or renal disease or any other condition known to interfere with the absorption, distribution, metabolism or excretion of drugs.
11. Subjects who have a definite or suspected personal history or family history of adverse reactions or hypersensitivity to the study drug or to drugs with a similar chemical structure.
12. Subject has body piercing of nipples or genitalia.

III.G.6. TREATMENTS

SB-207499 was provided as a 15 mg round, white tablet (Batch No. U97093). Matched placebo tablets (Batch No. U97090) were also supplied. The dosing regimen was one tablet twice daily for seven days. Dosing at home was confirmed by tablet counts and questioning of the subjects. On study days 1 (morning dose) and day 7 (both doses) all subjects were dosed within the Clinical Research Unit, Cambridge and each dose was witnessed by at least 2 medical/nursing staff.

Volunteers were instructed not to take any prescribed medication for a period of 14 days prior to or during the study. Over the counter medicines were also prohibited for 48 hours prior to and during the study. All prior and concomitant medication taken during the study was recorded with the indication, daily dose and dates of administration. Paracetamol was recommended for analgesia. Female volunteers were not permitted to use oral contraception or hormone replacement therapy. Volunteers were only permitted to take prescribed or other medication during this period if it was agreed in advance with the Principal Investigator who was satisfied that such medication would not compromise study safety or interfere with study procedures and results. [clinstat\147.pdf:21, 25-6]

III.G.7. VARIABLES

Blood samples from each time point over the day –1 to day 1 and day 7 to day 8, 24 hour periods were analyzed for prolactin, serum cortisol and ACTH. TSH and fasted glucose were measured using the 1000 hour sample on day –1 to day 7 sample. During these 24 hour sampling periods there was also complete urine collection for the measurement of urinary cortisol and creatinine. At each time point additional blood samples were stored for further hormone analysis. If a clinically important change was seen in prolactin, ACTH, serum cortisol levels, these samples were assayed for follicle stimulating hormone (FSH), TSH, luteinizing hormone (LH), oestradiol/testosterone [clinstat\147.pdf:33].

Hormone assays and parameters for the measurement of prolactin, ACTH, serum/urinary cortisol, TSH, creatinine and fasting glucose were performed. In each session, prolactin, ACTH and cortisol were measured over a 24 hour period prior to dosing on day 1 and 24 hours after dosing on day 7. Urinary cortisol over these 24 hour periods was measured, together with creatinine to facilitate cortisol: creatinine ratios. TSH and fasting glucose were measured using the 1000 hour samples on day –1 and day 7. Pharmacodynamic endpoints of interest were:

NDA #21573 (12/24/02, N-000) STUDY 147: PHARMACODYNAMIC ENDPOINT VARIABLES [clinstat\147.pdf:11]	
Endpoints	**Parameters**
Primary:	prolactin ($AUC_{0\text{-}24}$/24 on day 7)
Secondary:	ACTH and serum cortisol ($AUC_{0\text{-}24}$/24 on day 7) urinary cortisol (total measured from 0-24 hours on day 7)
Tertiary:	FSH, LH, TSH, glucose, testosterone/estradiol on day 7

Many of the hormones, including FSH, LH, and testosterone/estradiol were not assayed because no clinically important change was detected in any of the primary and secondary endpoints [clinstat\147.pdf:11].

Adverse experiences (AEs) were elicited by the investigator asking the subject a non-leading question such as "How do you feel?". Details of any elicited AEs and their severity, including any change in study drug administration, relationship to study drug, any corrective therapy given and outcome status were documented on the case report form. Relationship of AEs to study drug was judged by the investigator to be not related, unlikely, suspected, or probable. All adverse experiences were coded from the verbatim term according to the WHO Adverse Reaction Terminology (ART) dictionary by body system and preferred term. Semi-supine 12-lead ECG using a Schiller Cardiovit (Schiller AG, Switzerland) electrocardiograph was performed pre-study and pre-dose at each study session and at the follow up examination.

At pre-study screening, pre dose and at follow-up, volunteers had their semi-supine heart rate and systolic and diastolic blood pressure measured. Subjects rested in a semi-supine position for 10 minutes prior to each measurement. The criteria for determination of specific values of potential clinical concern for vital sign, 12-lead ECG, and safety laboratory data are presented in a referenced table. They do not warrant detailed replication in this small, one-week study review.

Any vital sign, 12-lead ECG, or safety laboratory values exceeding these pre-defined thresholds were identified by computer algorithm, flagged and tabulated in PIMS. Any such changes considered clinically significant were recorded as adverse experiences [clinstat\147.pdf:30-2].

III.G.8. STATISTICS

The primary and secondary pharmacodynamic endpoints of interest were analyzed by analysis of covariance (ANCOVA) fitting terms for sequence, gender, subject (gender-by-sequence), period, regimen and baseline (day-1 values). Point estimates and 95% confidence intervals for the differences "SB207499 - Placebo" were constructed using the residual variance from the ANCOVA. Point estimates and approximate 95% confidence intervals for the ratio of SB-207499/placebo were then obtained by dividing these point and interval estimates by the placebo least squares mean and adding 1.0 [clinstat\147.pdf:11].

III.G.9. DEMOGRAPHICS

Demographic characteristics of the healthy volunteers enrolled in this trial are shown in the following table. This was a study of young healthy male (n=10) and female (n=10) volunteers [clinstat\147.pdf:38].

NDA #21573 (12/24/02, N-000) STUDY 147: DEMOGRAPHIC CHARACTERISTICS [clinstat\147.pdf:39]				
Group	Parameter	Age (years)	Weight (kg)	Height (cm)
Pooled	n	20	20	20
	mean	33	1.71	72.26
	SD	7.8	0.09	10.29
	range	22-47	1.58-1.88	49.9-91.8

III.G.10. DISPOSITION

Twenty subjects were recruited of which 19 subjects received both regimens, SB-207499 and matching placebo. During the study one of the subjects (018) was withdrawn by the physician after having a hydrocortisone injection for tendinitis in her left thumb during the washout period. Subject 013 left the unit at 9am on day 7 of session 2 (SB-207499), 1 hour prior to completion of the 24 hour profiles for hormone parameters. Subjects 013 and 018 were excluded from the statistical analyses. The remaining 18 subjects completed the study as planned without any protocol deviations. [clinstat\147.pdf:38].

III.G.11. PRIOR & CONCOMITANT MEDICATIONS

None of the subjects took medication during a period of 14 days prior to the study start. Of the 47 adverse experiences reported, 9 required corrective treatment. Two subjects (007 and 009) received two doses of paracetamol (500 mg) for the treatment of headaches. In addition, a further three subjects (009, 022 and 021) received paracetamol (1G) for the treatment of headaches and earache respectively. Subject 009 also received ibuprofen for headache. Subject 002 suffered an acute tooth abcess and was prescribed Aspro Clear (aspirin) and metronidazole (200 mg). The Aspro Clear was taken four times a day for a period of 7 days and the metronidazole, three times a day for 8 days. During the study a protocol violation occurred (see Section 4.3) in which subject 018 was administered with a single hydrocortisone injection for tendinitis. The actual dose of this injection was unknown and the subject was withdrawn [clinstat\147.pdf:39].

III.G.12. EFFICACY (PHARMACODYNAMIC EVALUATION)

Mean serum levels of prolactin over 24 hours on days -1 and 7 were presented separately for males and females for each treatment group. Males on both day for both treatments had very similar mean prolactin levels (about 200 miu/L) that showed little fluctuation throughout the day. In females, the mean prolactin level was lowest at 10:00 am (about 200 miu/L), rising to a peak at the end of the day at midnight (about 300 miu/L). This pattern was apparently independent of the treatment and day of analysis, -1 or 7 [clinstat\147.pdf:46, 395].

Serum cortisol in both genders and regardless of treatment or day of analysis showed a zenith (200-400 nmol/L) at 10:00 am and a nadir at 10:00 pm to midnight (75-

100 nmol/L). ACTH showed changes similar in direction and timing to cortisol but with much more subdued excursions (range or means over 24 hours 10-30 pg/mL). Once again, there were no differences in serum ACTH with regard to gender, treatment or day of analysis [clinstat\147.pdf:46, 396-7].

Urinary cortisols collected over 24 hours for both days of analysis in males showed no treatment effect. In female patient 016, the day -1 placebo treatment was five times greater than the next highest level for that day, treatment and gender. For this reason, the summary table below uses medians and ranges to summarize the group data [clinstat\147.pdf:561].

NDA #21573 (12/24/02, N-000) STUDY 147: MEDIAN (RANGE) 24-HOUR URINARY CORTISOLS [clinstat\147.pdf:561]			
Day -1		Day 7	
Ariflo	Placebo	Ariflo	Placebo
MALES (n=10/treatment)			
87 (28-220)	90 (22-150)	78 (39-110)	91 (39-120)
FEMALES (n=8/treatment)			
50 (22-150)	65 (30-660)	50 (LOQ-130)	51 (LOQ-88)

None of these variables showed any difference between genders and treatments over time. However, this was a very small study carried out for a very short time. The apparent reassurance that these results offer must be considered with appreciation for the limited ability of even a very large number of patients to demonstrate a systemic effect of physiological consequence; e.g., growth suppression in children with inhaled and nasal corticosteroids in the absence of a signal from any conventionally accepted tests of the HPA axis.

Creatinine, TSH and glucose were also measured but were not summarized in the report. Inspection of the tables presented by treatment, gender and day did not reveal any systematic effect [clinstat\147.pdf:365-88].

III.G.13. SAFETY

III.G.13.a. ADVERSE EVENTS (AES)

A total of 47 adverse experiences were reported by 20 subjects and most occurred after the administration of SB-207499. The following table presents the most frequent AEs which occurred with a frequency of two or more in either treatment group. Only study AEs and not prior or pre-existing signs and symptoms are included [clinstat\147.pdf:41-2].

NDA #21573 (12/24/02, N-000) STUDY 147: ADVERSE EVENTS [clinstat\147.pdf:42]		
Adverse Events	Number of Subjects	
	Ariflo 15 mg twice daily	Placebo
Number of subjects exposed	19	20

NDA #21573 (12/24/02, N-000) STUDY 147: ADVERSE EVENTS [clinstat\147.pdf:42]		
Adverse Events	Number of Subjects	
	Ariflo 15 mg twice daily	Placebo
Total number of AEs	38	9
Number of subjects with AEs	15	5
back pain	2	0
diarrhea	4	0
flatulence	3	0
headache	12	2
nausea	6	1
pain	2	0

III.G.13.b. DEATHS

None [clinstat\147.pdf:43].

III.G.13.c. WITHDRAWALS DUE TO AES

None [clinstat\147.pdf:43].

III.G.13.d. SERIOUS ADVERSE EVENTS (SAES)

None [clinstat\147.pdf:43].

III.G.13.e. VITAL SIGNS

None outside of the normal range [clinstat\147.pdf:43, 111-31].

III.G.13.f. ELECTROCARDIOGRAMS (ECGS)

None outside of the normal range [clinstat\147.pdf:44, 135-58].

III.G.13.g. LABORATORIES

Hematology, chemistry and routine and microscopic urinalysis were reported in line listing for each patient. By inspection the most common but infrequent finding outside the range of normal was elevated cholesterol [clinstat\147.pdf:44, 160-318].